TRANSACTIONS

AMERICAN ACADEMY
of
OPHTHALMOLOGY
and
OTOLARYNGOLOGY

FORTY-FIFTH
ANNUAL MEETING

A. D. RUEDEMANN, M.D.
General Chairman of Arrangements

HOTEL CLEVELAND
CLEVELAND, OHIO
October 6 to 11, 1940

Editorial Board

William L. Benedict, M.D., *Editor in Chief*, Rochester, Minnesota

W. P. Wherry, M.D., *Business Manager*, Omaha, Nebraska

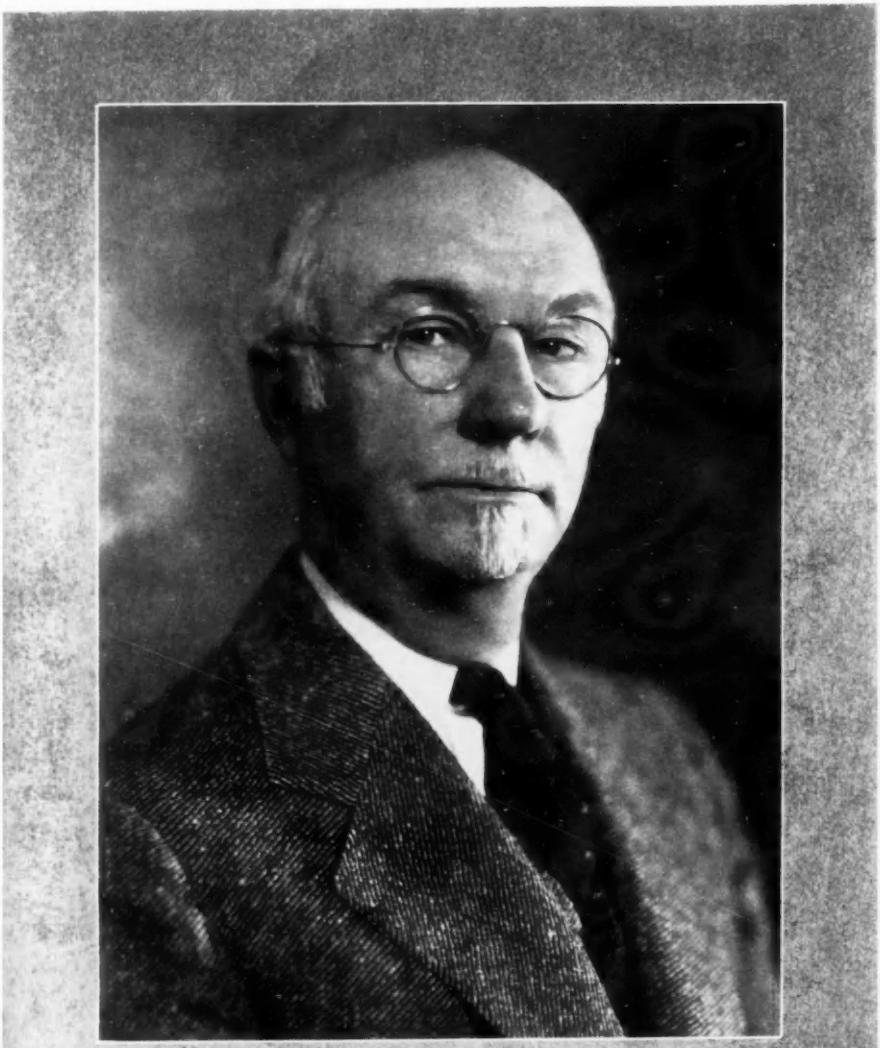
W. H. Morrison, M.D., *Associate Editor*, Omaha, Nebraska

The Board of Secretaries

Printed by
Douglas Printing Company, Omaha, Nebraska

PRINTED IN THE UNITED STATES OF AMERICA

Medical
Library
1941
3306



President 1940

Frank P. Bradley

CHICAGO, ILLINOIS

Guest of Honor, 1940

SECORD H. LARGE, M.D.

CLEVELAND, OHIO

OFFICERS *for* 1940

FRANK E. BRAWLEY, M.D., Chicago, Illinois
President
ARTHUR W. PROETZ, M.D., St. Louis, Missouri
First Vice-President
FRANK R. SPENCER, M.D., Boulder, Colorado
President-Elect
JOSEPH F. DUANE, M.D., Peoria, Illinois
Second Vice-President
C. T. PORTER, M.D., Boston, Massachussetts
Third Vice-President
S. H. LARGE, M.D., Cleveland, Ohio
Comptroller

BOARD *of* SECRETARIES
EDITORIAL BOARD

WILLIAM P. WHERRY, M.D., Omaha, Nebraska
Executive Secretary-Treasurer
WILLIAM L. BENEDICT, M.D., Rochester, Minnesota
Secretary for Ophthalmology
JOHN L. MYERS, M.D., Kansas City, Missouri
Secretary for Otolaryngology
DEAN M. LIERLE, M.D., Iowa City, Iowa
Secretary for Instruction — Otolaryngology
A. D. RUEDEMANN, M.D., Cleveland, Ohio
Secretary for Instruction — Ophthalmology
ERLING W. HANSEN, M.D., Minneapolis, Minnesota
Secretary for Public Relations

COUNCIL

FRANK E. BRAWLEY, M.D. (1943), Chicago, Illinois
ARTHUR W. PROETZ, M.D. (1940), St. Louis, Missouri
FRANK R. SPENCER, M.D. (1944), Boulder, Colorado
L. W. DEAN, M.D. (1940), St. Louis, Missouri
HARRY S. GRADLE, M.D. (1941), Chicago, Illinois
GEORGE M. COATES, M.D. (1942), Philadelphia, Pa.
SECORD H. LARGE, M.D., Cleveland, Ohio
MARVIN F. JONES, M.D. (1940), New York, N. Y.
LAWRENCE T. POST, M.D. (1941), St. Louis, Missouri
CARL H. McCASKEY, M.D. (1942), Indianapolis, Indiana
ALBERT C. SNELL, M.D. (1943), Rochester, N. Y.

Ex-Officio Members *of* Council

BOARD OF SECRETARIES
ALLEN GREENWOOD, M.D., Boston, Massachusetts
Liaison Officer, Honor Society

Teachers' Section

A. D. RUEDEMANN, M.D., *Secretary*, Cleveland, Ohio

COMMITTEES FOR 1940

Council Committees

Executive

L. W. Dean, M.D., Chairman	New York, N. Y.
Harry S. Gradle, M.D.	Chicago, Ill.
George M. Coates, M.D.	Philadelphia, Pa.
Secord H. Large	Cleveland, Ohio
W. P. Wherry, M.D.	Omaha, Nebr.

General Activities

Marvin F. Jones, M.D., Chairman	New York, N. Y.
Lawrence T. Post, M.D.	St. Louis, Mo.
Carl H. McCaskey, M.D.	Indianapolis, Ind.
Albert C. Snell, M.D.	Rochester, N. Y.
Frank R. Spencer, M.D.	Boulder, Colo.
Arthur W. Proetz, M.D.	St. Louis, Mo.

Research and Finance

George M. Coates, M.D., Chairman	Philadelphia, Pa.
Lee W. Dean, M.D.	St. Louis, Mo.
Harry S. Gradle, M.D.	Chicago, Ill.

Judicial

Lee W. Dean, M.D., Chairman	St. Louis, Mo.
George M. Coates, M.D.	Philadelphia, Pa.
Marvin F. Jones, M.D.	New York, N. Y.

Ex-Officio Investment Committee

Frank E. Burch, M.D., Chairman	St. Paul, Minn.
Lee W. Dean, M.D.	St. Louis, Mo.
S. H. Large, M.D.	Cleveland, Ohio
W. P. Wherry, M.D.	Omaha, Nebr.

Standing Committees

American Board of Ophthalmology

Frederick C. Cordes, M.D. Grady E. Clay, M.D.
W. L. Benedict, M.D. C. S. O'Brien, M.D.

American Board of Otolaryngology

Thomas E. Carmody, M.D. W. P. Wherry, M.D.

Historian

James A. Babbitt, M.D.

Ophthalmic Pathology

Harry S. Gradle, M.D., Chairman
F. H. Verhoeff, M.D. J. S. Friedenwald, M.D.
Georgiana Dvorak-Theobald, M.D.

Otolaryngic Pathology

Joseph C. Beck, M.D., Chairman
Frank J. Novak, Jr., M.D. LeRoy A. Schall, M.D.
Herman Z. Semenov, M.D.

Committee on Conservation of Hearing

Horace Newhart, M.D., Chairman

James A. Babbitt, M.D.	A. A. Hayden, M.D.
John F. Barnhill, M.D.	Frederick T. Hill, M.D.
Gordon Berry, M.D.	Marvin F. Jones, M.D.
T. E. Carmody, M.D.	Edward King, M.D.
E. H. Cary, M.D.	Dean M. Lierle, M.D.
George M. Coates, M.D.	C. Stewart Nash, M.D.
L. W. Dean, M.D.	Ernest M. Seydell, M.D.
Howard V. Dutrow, M.D.	Burt R. Shurly, M.D.
A. C. Furstenberg, M.D.	Harry A. Smith, M.D.
Max A. Goldstein, M.D.	H. M. Taylor, M.D.
William A. Grove, M.D.	Claude T. Uren, M.D.

The American Association for the Advancement of Science

Official Delegate: Harry S. Gradle, M.D., Chicago, Ill.

National Society for Prevention of Blindness

Liaison Committee

W. H. Luedde, M.D. St. Louis, Mo.
A. O. Pfingst, M.D. Louisville, Ky.

Ophthalmic Literature

Conrad Berens, M.D. Grady E. Clay, M.D.
Harry S. Gradle, M.D.

TEACHERS' SECTION

Secretary in Charge — A. D. Ruedemann, M.D.

Advisory Committee Visual Defects and Civil Service

Benjamin Rones, M.D., *Chairman*
Alfred Cowan, M.D. Grady Clay, M.D.

Representatives of the Academy on Joint Committees

American Committee on Optics and Visual Physiology

Charles A. Bahn, M.D. W. L. Benedict, M.D.
Frederick Cordes, M.D.

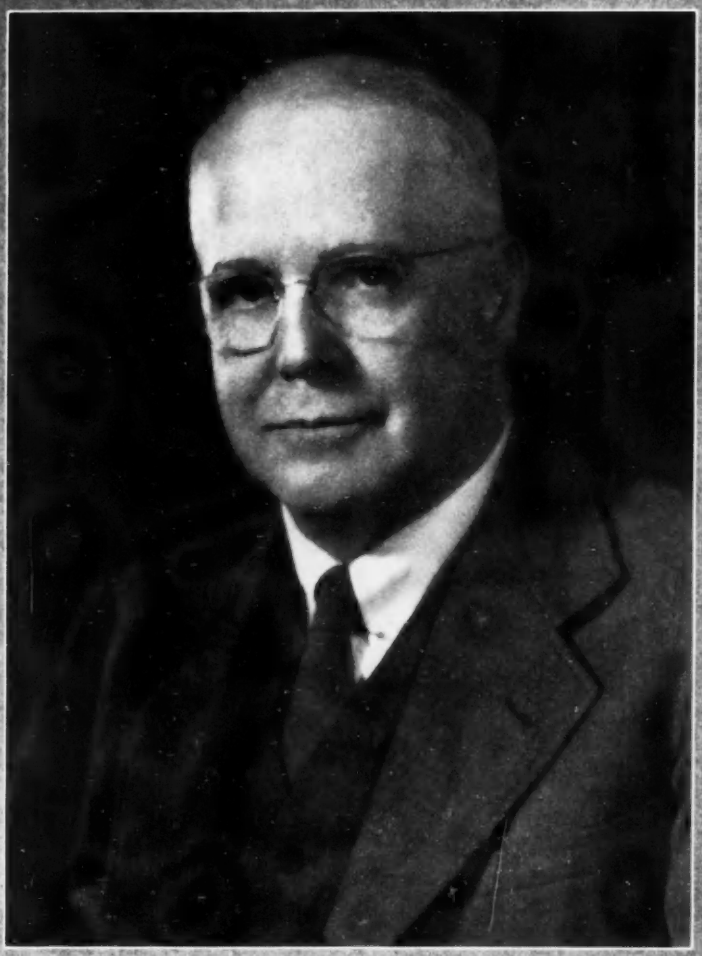
Eye Health Committee of the American Student Health Association

Advisory Committee

W. L. Benedict, M.D., Chairman Rochester, Minn.

Orthoptics

Grady E. Clay, M.D. A. de H. Prangen, M.D.
LeGrand H. Hardy, M.D.



President 1941

Frank R. Spencer

BOULDER, COLORADO

OFFICERS *for* 1941

FRANK R. SPENCER, M.D., Boulder, Colorado
President
EVERETT L. GOAR, M.D., Houston, Texas
First Vice-President
RALPH I. LLOYD, M.D., Brooklyn, New York
President-Elect
JAMES M. ROBB, M.D., Detroit, Michigan
Second Vice-President
RALPH O. RYCHENER, M.D., Memphis, Tennessee
Third Vice-President
SECORD H. LARGE, M.D., Cleveland, Ohio
Comptroller

BOARD OF SECRETARIES

WILLIAM P. WHERRY, M.D., Omaha, Nebraska
Executive Secretary-Treasurer
WILLIAM L. BENEDICT, M.D., Rochester, Minnesota
Secretary for Ophthalmology
JOHN L. MYERS, M.D., Kansas City, Missouri
Secretary for Otolaryngology
DEAN M. LIERLE, M.D., Iowa City, Iowa
Secretary for Instruction — Otolaryngology
A. D. RUEDEMANN, M.D., Cleveland, Ohio
Secretary for Instruction — Ophthalmology
ERLING W. HANSEN, M.D., Minneapolis, Minnesota
Secretary for Public Relations
O. E. VAN ALYEA, M.D., Chicago, Illinois
Assistant Secretary

COUNCIL

FRANK R. SPENCER, M.D. (1944), Boulder, Colorado
EVERETT L. GOAR, M.D. (1941), Houston, Texas
RALPH I. LLOYD, M.D. (1945), Brooklyn, New York
HARRY S. GRADLE, M.D. (1941), Chicago, Illinois
GEORGE M. COATES, M.D. (1942), Philadelphia, Pa.
FRANK E. BRAWLEY, M.D. (1943), Chicago, Illinois
SECORD H. LARGE, M.D., Cleveland, Ohio
LAWRENCE T. POST, M.D. (1941), St. Louis, Missouri
CARL H. McCASKEY, M.D. (1942), Indianapolis, Indiana
ALBERT C. SNELL, M.D. (1943), Rochester, N. Y.
J. McKENZIE BROWN, M.D. (1944), Los Angeles, California

EX-OFFICIO MEMBERS *of* COUNCIL

BOARD OF SECRETARIES
ALLEN GREENWOOD, M.D., Boston, Massachusetts
Liaison Officer, Honor Society

TEACHERS' SECTION

A. D. RUEDEMANN, M.D., *Secretary*, Cleveland, Ohio

COMMITTEES FOR 1941

Council Committees

Executive

Harry S. Gradle, M.D., Chairman	Chicago, Ill.
George M. Coates, M.D.	Philadelphia, Pa.
Frank E. Brawley, M.D.	Chicago, Ill.
Frank R. Spencer, M.D.	Boulder, Colo.
Secord H. Large, M.D.	Cleveland, Ohio
W. P. Wherry, M.D.	Omaha, Nebr.

General Activities

Lawrence T. Post, M.D., Chairman	St. Louis, Mo.
C. H. McCaskey, M.D.	Indianapolis, Ind.
Albert C. Snell, M.D.	Rochester, N. Y.
J. McKenzie Brown, M.D.	Los Angeles, Calif.
Ralph I. Lloyd, M.D.	Brooklyn, N. Y.
Everett L. Goar, M.D.	Houston, Texas

Research and Finance

Frank E. Brawley, Chairman	Chicago, Ill.
George M. Coates, M.D.	Philadelphia, Pa.
Harry S. Gradle, M.D.	Chicago, Ill.

Judicial

Harry S. Gradle, Chairman	Chicago, Ill.
Lawrence T. Post, M.D.	St. Louis, Mo.
Frank E. Brawley, M.D.	Chicago, Ill.

Ex-Officio Investment Committee

Frank E. Burch, M.D., Chairman	St. Paul, Minn.
Lee W. Dean, M.D.	St. Louis, Mo.
S. H. Large, M.D.	Cleveland, Ohio
W. P. Wherry, M.D.	Omaha, Nebr.

Standing Committees

American Board of Ophthalmology

Frederick C. Cordes, M.D. Grady E. Clay, M.D.
W. L. Benedict, M.D. C. S. O'Brien, M.D.

American Board of Otolaryngology

T. E. Carmody, M.D. W. P. Wherry, M.D.

Historian

James A. Babbitt, M.D.

Ophthalmic Pathology

Harry S. Gradle, M.D., Chairman
F. H. Verhoeff, M.D. J. S. Friedenwald, M.D.
Georgiana Dvorak-Theobald, M.D.

Otolaryngic Pathology

Joseph C. Beck, M.D., Chairman
Frank J. Novak, Jr., M.D. LeRoy A. Schall, M.D.
Herman Z. Semenov, M.D.

Committee on Conservation of Hearing

Horace Newhart, M.D., Chairman

James A. Babbitt, M.D.	William A. Grove, M.D.
John F. Barnhill, M.D.	Frederick T. Hill, M.D.
Gordon Berry, M.D.	Marvin F. Jones, M.D.
T. E. Carmody, M.D.	Edward King, M.D.
E. H. Cary, M.D.	Dean M. Lierle, M.D.
George M. Coates, M.D.	C. Stewart Nash, M.D.
L. W. Dean, M.D.	Ernest M. Seydell, M.D.
Howard V. Dutrow, M.D.	Burt R. Shurly, M.D.
A. C. Furstenberg, M.D.	Harry A. Smith, M.D.
Max A. Goldstein, M.D.	H. Marshall Taylor, M.D.

The American Association for the Advancement of Science

Official Delegate: Harry S. Gradle, M.D., Chicago, Ill.

Scientific Exhibit

O. E. Van Alyea, M.D., Chairman Chicago, Ill.
Georgiana Dvorak-Theobald, M.D., Consult. Chicago

National Society for Prevention of Blindness

Liaison Committee

W. H. Luedde, M.D.	St. Louis, Mo.
A. O. Pfingst, M.D.	Louisville, Ky.

Advisory Committee Visual Defects and Civil Service

Benjamin Rones, M.D., *Chairman*
Alfred Cowan, M.D. Grady Clay, M.D.

Ophthalmic Literature

Conrad Berens, M.D. Grady E. Clay, M.D.
Harry S. Gradle, M.D.

TEACHERS' SECTION

Secretary in Charge — A. D. Ruedemann, M.D.

Representatives of the Academy on Joint Committees

American Committee on Optics and Visual Physiology

Charles A. Bahn, M.D. W. L. Benedict, M.D.
Frederick Cordes, M.D.

Eye Health Committee of the American Student Health Association

Advisory Committee

W. L. Benedict, M.D., *Chairman*, Rochester, Minn.

The American Orthoptic Council

A. de H. Prangen, M.D. LeGrand H. Hardy, M.D.
John B. Hitz, M.D.

President-Elect, 1940
FRANK R. SPENCER, M.D.
BOULDER, COLORADO

President-Elect, 1941
RALPH I. LLOYD, M.D.
BROOKLYN, NEW YORK

First Vice-President, 1940
ARTHUR W. PROETZ, M.D.
ST. LOUIS, MISSOURI

First Vice President, 1941
EVERETT L. GOAR, M.D.
HOUSTON, TEXAS

Second Vice-President, 1940
JOSEPH F. DUANE, M.D.
PEORIA, ILLINOIS

Second Vice President, 1941
JAMES M. ROBB, M.D.
DETROIT, MICHIGAN

Third Vice-President, 1940
C. T. PORTER, M.D.
Boston, Massachusetts

Third Vice-Presidnet, 1941
RALPH O. RYCHENER, M.D.
Memphis, Tennessee

Executive Secretary-Treasurer
1940 - 1941
WILLIAM P. WHERRY, M.D.
Omaha, Nebraska

Comptroller
1940 - 1941
S. H. LARGE, M.D.
Cleveland, Ohio

Secretary for Ophthalmology
1940 - 1941
WILLIAM L. BENEDICT, M.D.
Rochester, Minnesota

Secretary for Otolaryngology
1940 - 1941
JOHN L. MYERS, M.D.
Kansas City, Missouri

Secretary for Public Relations
1940 - 1941
ERLING W. HANSON, M.D.
MINNEAPOLIS, MINNESOTA

Secretary for Instruction
Otolaryngology
1940 - 1941
DEAN M. LIERLE, M.D.
IOWA CITY, IOWA

Secretary for Instruction
Ophthalmology
1940 - 1941
A. D. RUEDEMANN, M.D.
CLEVELAND, OHIO

Assistant Secretary, 1941
O. E. VAN ALYEA, M.D.
CHICAGO, ILLINOIS

Associate Editor
Transactions, 1941
W. HOWARD MORRISON, M.D.
OMAHA, NEBRASKA

PAST PRESIDENTS

1896 — Adolph Alt, M.D. ..... St. Louis, Mo.
1897 — Adolph Alt, M.D. ..... St. Louis, Mo.
1898 — B. E. Fryer, M.D. ..... Kansas City, Mo.
1899 — J. E. Colburn, M.D. ..... Chicago, Ill.
1900 — W. Scheppegrell, M.D. ..... St. Louis, Mo.
1901 — M. A. Goldstein, M.D. ..... St. Louis, Mo.
1902 — C. R. Holmes, M.D. ..... Cincinnati, Ohio
1903 — W. L. Ballenger, M.D. ..... Chicago, Ill.
1904 — Edward Jackson, M.D. ..... Denver, Colo.
1905 — Hanau Loeb, M.D. ..... St. Louis, Mo.
1906 — Casey Wood, M.D. ..... Chicago, Ill.
1907 — J. A. Stucky, M.D. ..... Lexington, Ky.
1908 — Derrick Vail, M.D. ..... Cincinnati, Ohio
1909 — Otto Stein, M.D. ..... Chicago, Ill.
1910 — Wendell Reber, M.D. ..... Philadelphia, Pa.
1911 — J. J. Kyle, M.D. ..... Indianapolis, Ind.
1912 — George F. Suker, M.D. ..... Chicago, Ill.
1913 — J. W. Murphy, M.D. ..... Cincinnati, Ohio
1914 — J. M. Ray, M.D. ..... Louisville, Ky.
1915 — Joseph Beck, M.D. ..... Chicago, Ill.
1916 — J. E. Brown, M.D. ..... Columbus, Ohio
1917 — W. L. Dayton, M.D. ..... Lincoln, Nebr.

PAST PRESIDENTS

* * *

1918 — Allen Greenwood, M.D. ..... Boston, Mass.
1919 — J. M. Ingersoll, M.D. ..... Cleveland, Ohio
1920 — L. M. Francis, M.D. ..... Buffalo, N. Y.
1921 — Emil Mayer, M.D. ..... New York, N. Y.
1922 — Walter R. Parker, M.D. ..... Detroit, Mich.
1923 — Thomas E. Carmody, M.D. ..... Denver, Colo.
1924 — Walter B. Lancaster, M.D. ..... Boston, Mass.
1925 — Horace Newhart, M.D. ..... Minneapolis, Minn.
1926 — E. C. Ellett, M.D. ..... Memphis, Tenn.
1927 — Ross Hall Skillern, M.D. ..... Philadelphia, Pa.
1928 — Luther C. Peter, M.D. ..... Philadelphia, Pa.
1929 — Harris P. Mosher, M.D. ..... Boston, Mass.
1930 — William H. Wilder, M.D. ..... Chicago, Ill.
1931 — John F. Barnhill, M.D. ..... Miami Beach, Fla.
1932 — S. Hanford McKee, M.D. ..... Montreal, Canada
1933 — Burt R. Shurly, M.D. ..... Detroit, Mich.
1934 — John M. Wheeler, M.D. ..... New York, N. Y.
1935 — Wells P. Eagleton, M.D. ..... Newark, N. J.
1936 — Frank E. Burch, M.D. ..... St. Paul, Minn.
1937 — Lee W. Dean, M.D. ..... St. Louis, Mo.
1938 — Harry S. Gradle, M.D. ..... Chicago, Ill.
1939 — George M. Coates, M.D. ..... Philadelphia, Pa.
1940 — Frank R. Brawley, M.D. ..... Chicago, Ill.

THE PROPOSED FORMATION OF A PAN-AMERICAN OPHTHALMOLOGICAL SOCIETY

FRANK E. BRAWLEY, M.D.
CHICAGO

BEFORE presenting my address, permit me to digress for a moment to express to the members of the Academy and to the fine group of officers and members of the Council my deep appreciation of the great honor which I have received at your hands. The post of President of the Academy is one of the highest honors one may attain in the Medical world, and I am deeply sensible of the privilege which has been accorded me.

It is a tradition of the Academy that each annual meeting be initiated with an address by the President. In these addresses there has been presented a scope of subjects which has ranged from scientific information, germane to our specialties, to new ideas on activities designed to improve the usefulness of our Society.

This year I have chosen what seems to be a most timely subject — The Proposed Formation of a Pan-American Ophthalmological Society. The status of world affairs, especially in Europe, is bound to affect the future of the International Ophthalmological Society. In fact, it is doubtful if that Society will ever function again in its original form.

Therefore, the Council of the Academy consented to sponsor the organization of an Ophthalmological Society to be composed of representative ophthalmologists from all of the twenty-one Republics of the Western Hemisphere, as originally proposed by Doctor Harry S. Gradle. The preliminary work has been very well carried out by a Committee which consists of Doctor Conrad Berens and Doctor Moacyr Alvaro, with Doctor Harry S. Gradle as Chairman. On Friday and Saturday of this week, the first Pan-American Ophthalmological Society will hold its first meeting, and it is hoped that as many as possible of the Academy members will be present.

The idea of an International Ophthalmological Congress was conceived many years ago. Mr. E. Worlemont, of Brussels, Belgium, was the first to suggest such an Organization, and the initial meeting was held in Brussels in 1857. Subsequently, meetings were held every four years, and many outstanding ophthalmologists were included in the membership list. Such men as V. Graefe, Donders, Bowman, Galezowski, Javal, Helmholtz, Warren Tay, and Jonathan Hutchinson represented the European countries; Cornelius R. Agnew, John Green, and Herman Knapp were among the representatives from the United States.

There is very little information with regard to the activities of the International Congress in the earlier reports of its meetings, and I am greatly indebted to Doctor Harry Gradle for the record of the course of events from 1914 to date.

The Congress was scheduled to meet in St. Petersburg, Russia, in August, 1914. Unfortunately, this meeting was intercepted by the War. Following peace negotiations in 1918, endeavors to re-

Address of the President of the American Academy of Ophthalmology and Otolaryngology. Presented at the Forty-Fifth Annual Session, October 6 to 10, 1940, Cleveland, Ohio.

vive the International Ophthalmological Congress met with violent opposition by both the French and the Germans. Finally, a committee which was more or less self-appointed, consisting of George de Schweinitz, Walter R. Parker, Treacher Collins, and J. van der Hoeve promulgated an International Ophthalmological Congress of English-speaking countries which met in Washington in April, 1922. A second Congress was held in London in 1925, and this also consisted of English-speaking countries. The International Congress Committee was a direct development of these two meetings. The first post-war International Congress was held in Amsterdam in 1929, under the chairmanship of J. van der Hoeve. R. Marx, of Rotterdam, was secretary. This was the most largely attended International Congress ever to be held to date. The following meeting was held in Madrid, in 1933, and the last meeting of the Congress was held in Egypt in December, 1937. Professor Nordenson, of Stockholm, was the chairman at that time.

Vienna was chosen as the meeting place for the 1941 Congress in spite of the fact that invitations from Poland and the United States had been issued. The invitation from the United States had been well received, however. As Naziism increased and Austria was taken over by Germany, many protests were received by the International Committee against holding the 1941 meeting in any except a neutral country. Nordenson stated that refusal to live up to the agreement to hold the meeting in Vienna would be an offense to the German government. At the meeting of the Committee in London, in April, 1939, confirmation was made to the effect that the meeting of the 1941 Congress be held in Vienna. There were positive assertions that no English, French, Belgian, Dutch, or American Ophthalmologists would attend. Naturally, the plans for the meeting of the 1941 Congress have been entirely dissipated at this time because of the present War conditions in Europe. So that an International forum would be continued, the Pan-American Congress was formulated.

Rapprochement between the Latin-American countries and our own country is being fostered in many ways. The more I learned of these activities while gathering material for this address, the more amazed I became at their extent.

The first International Conference of American States was held in Washington, D. C., fifty years ago. The Organization, now known as the Pan-American Union, has as its objective the promotion of closer relations in intellectual, cultural, economic, juridical, and social fields. Incidentally, the Pan-American Union is now housed in one of Washington's most beautiful buildings. The American Republics are giving to the world a fine example of uninterrupted, scientific activity in an atmosphere of peace and unselfish collaboration.

It is of interest to note that in addition to official governmental activities, many private organizations in the United States are engaged in promoting better friendly relations with our Latin-American neighbors. One of the outstanding achievements in this respect is the John Simon Guggenheim Memorial Foundation which has created fellowships each year since 1925 to aid research workers in all fields as well as creative workers in the field of fine arts. Eleven years ago the Foundation instituted fellowship awards to Latin-American scholars to be used to carry on their studies here. Similar fellowship awards were made to an approximately equal number of citizens of this country to further their work in Latin-American countries. The average annual stipend is two thousand dollars. For 1940 and 1941 nineteen such fellowship awards were made, six of which were

to Latin-Americans. There has been no effort to make this Foundation an Organization which even remotely sponsors any form of National propaganda. The purpose of the Guggenheim Memorial Foundation is the outgrowth of a deep conviction of John Simon Guggenheim that a better understanding among the people of the Western Hemisphere will be promoted out of a knowledge of each other's culture.

In August of this year, approximately one hundred and fifty professors from Latin-American countries attended the Second International Congress of Professors of Ibero-American Literature held in Los Angeles. Doctor Manuel Gonzalez of Los Angeles served as President at this meeting.

Music as a universal language is an ideal medium for developing friendly relations and understanding. Leopold Stokowski is scheduled to make a goodwill tour of Latin-America with the All-American Youth Orchestra recruited from all the States of the Union.

Furthermore, the Latin-American Exhibition of Fine Arts was held this summer at the Riverside Museum in New York. This exhibit was presented at the Riverside Museum to the public for the first time in 1939. Following the exhibition in New York, a successful tour of the United States was made.

The Institute of Latin-American Studies was sponsored this summer at the University of Texas. As part of the Institute's activities, a conference on Latin-American culture was held on July 1. Fifty instructors in Latin-American subjects assembled, representing the States of Arkansas, Colorado, Kansas, Louisiana, Missouri, New Mexico, Oklahoma, and Texas. This was the second meeting which the Committee on Latin-American Studies has jointly sponsored, the first meeting having been held at the University of Michigan in the summer of 1939. The University of Texas considers this Institute permanent. The library of the University of Texas contains 42,000 books and pamphlets and over a million pages of original manuscripts pertaining to Latin-American literature.

As far back as 1935, Latin-American activities were showing evidence of progress, at which time the Pan-American Child Congress was held in Mexico City.

The various activities which year by year have been increasing and expanding also have led to an interchange of ideas and knowledge about tropical agriculture, economics, and control of racial and cultural problems which should prove useful to all the American Republics.

One of the most recent efforts to promote Pan-American unity is the project of the Reader's Digest in publishing editions of their periodicals translated from English to Spanish. The publishers solicit subscriptions at the minimal cost of one dollar. This gesture of goodwill is far-reaching in its effort to foster friendly relations between the people of the United States and those of the Latin-American countries. A list of Latin-American groups has been compiled so that doctors, lawyers, teachers, and others in the United States wishing to send gift subscriptions to members of similar groups in Latin-America will have access to accurate names and addresses which will thereby facilitate the proper handling of the mail delivery of the issues. This announcement appeared in the August, 1940, number of the Reader's Digest, and the Spanish edition will begin with the November, 1940, number. The person ordering the Reader's Digest pays the fee of one dollar, and the publishers discount the remaining two dollars of the usual subscription price.

As far as the radio is concerned, in Hollywood five motion picture companies are producing attractive programs which are electrically transcribed and sent East to the Columbia Broadcasting Company where they are broadcast to Latin-America by short wave in competition with German and Italian programs.

In the field of Medicine, however, a great deal has not been done to develop Pan-American relationships. Only since 1928 has the Pan-American Medical Association been in existence. It is an ambitious and comprehensive Society, however, and the roster of its Officers and Section Officials constitutes a large medical society in itself. The Section on Ophthalmology at the last Cruise Congress which was held in 1938 was under the able Presidency of the late Doctor Webb W. Weeks. With him were associated many of our friends in the Academy, namely, Doctors Arnold Knapp, S. Hanford McKee, Walter Lancaster, and Ramon Castroviejo, who served as Vice Presidents. Doctor David H. Webster was the Secretary. Members of the Executive Committee were: Chairman, Doctor R. E. Meek, Doctors John O. McReynolds, Edward Ellett, Harry M. Weed, Conrad Berens, and Derrick Vail, Jr.

Another medical representation of unity among the American Republics is the Pan-American Conference of National Directors of Health. At their last meeting held in Washington, D. C., in May, 1940, Doctor Thomas Parran, Surgeon-General of the Army, made the following statement:

> The strength of any nation in modern war depends not only on its armies, its battleships, and its air forces; it depends upon the health and vigor of its citizenship.
>
> To lift from our people the load of preventable disease, to insure adequate nutrition of the masses, to free our nations from the large and unseen tax for the care of the unfit, to provide opportunities for healthful living may, in the long run, be more important as a means of defense than are instruments of war. These objectives are of equal importance for the peaceful progress of our nations.

So far as I am able to ascertain, the first effort to ally interest in Latin-American Medicine in the United States was made in 1920 by Doctor Franklin Martin. At that time he was Director-General of the American College of Surgeons. Doctor Martin, together with Doctor William J. Mayo, visited South America, and they stopped at Jamaica, Panama, Peru, Chile, Argentina, and Uruguay. The following year, Doctor Martin again traveled to South America, and at that time he was accompanied by Doctor Thomas Watkins, of Chicago. They visited the same countries as previously, and added Brazil to the itinerary. On his return, Doctor Martin published a book of about three hundred pages, describing the hospitals and clinics which had been visited. He and his associates were unanimous in their praises of the high standards which were observed in the hospitals and the surgical practices which in their opinion equaled those of any country in the world.

More recent advances in Latin-American Medicine should be mentioned here. The Medical School of the University of Havana has developed a Department of Parasitology ranked as the best in the world. In Brazil, the Chagas Institute has done excellent work with regard to the treatment of dysenteries peculiar to people of South American countries. In Brazil is found also the Butantan Institute where serums for use in the treatment of snakebites have been perfected. The realization of the importance of this work to the people of the United States has resulted in the establishment of such a Medical Base here.

For many years after the great liberator, Simon Bolivar, was instrumental in bringing freedom in Government to the

South American countries, the people continued to refer to the Old World for their cultural standards. During the time of early American history, we followed the customs of England, while Latin-America remained in close contact with France, Spain, and Portugal. With the productive, economic, and political growth in the Western Hemisphere, it is evident that an independent culture from that of Europe is developing.

During these times of world chaos, more than ever it is important to strive for understanding and a free exchange of ideas among the twenty-one American Republics. In considering the difficulties which beset the paths of our National leaders in adjusting the many economic problems, the obstacles to full and complete understanding and cooperation in the field of Medicine seem insignificant.

In conclusion, I hope that the members of the Academy may be greatly inspired to sponsor the Pan-American Ophthalmological Society, and I am sure that you all join me in wishing this new Society a brilliant and useful future.

SOME MEDICAL PHASES OF YESTERDAY AND TODAY

Address of the Guest of Honor

SECORD H. LARGE, M.D.
CLEVELAND

Mr. President, Guests, and Fellow Members of the Academy:

IF PRECEDENT were being followed you would now be having the pleasure of hearing an address by an Ophthalmologist. Not being an Ophthalmologist, but nevertheless having been honored by you in choosing me as your guest of honor, I feel that it would not be fitting for me to speak to you on a purely otolaryngological subject. Instead, with your permission, I should like to recall some past experiences and look forward to the solution of some of the problems that are besetting Medicine today. For the great honor which you have done me, I am humbly and deeply appreciative and wish to thank you one and all.

Back in the gay nineties I began the practice of Medicine in a small town in Canada, many miles from any large center. The handicaps were great. There were no hospital facilities, no medical societies, no medical libraries, no laboratories, and none of the nicer refinements that today aid us in making a diagnosis.

Calomel and quinine were the two most popular drugs. Vaccines were limited to that for smallpox. Surgery was done on the kitchen table with chloroform as the anesthetic of choice. Rubber gloves had not yet come into use. Obstetrical cases were delivered with the help of a neighbor's wife, a few fruit jars filled with hot water, and a kerosene lamp. Diphtheria antitoxin was on the market but in insufficient quantities to supply the outlying parts of the country. Too often we were forced to rely on the tracheotomy tube and supporting treatments. The mortality rate was appalling. Typhoid fever was with us at all times. Preventive Medicine had made little headway, and it was difficult to persuade the laity to accept anything new, even the simple procedure of boiling the drinking water. Life in that age was not strenuous. The country folk enjoyed peace and tranquillity. The "nervous breakdown" era had not reached them. Insomnia was rare. It was a day of wide-open spaces with one's territory extending twenty-five miles from the office, the distance to be covered via horse and buggy.

The graduating classes from the medical schools were large, and the opportunities for internships in hospitals so few that most of the newly graduated doctors started in practice with some book learning and very little actual experience.

How different is the picture today! The medical schools have a much higher standard, and the classes are limited. Most young doctors realize that the proper preparation for the practice of Medicine requires some years residency in a high-grade hospital. In spite of the added number of years required for preparation, the increased expense and the keen competition, our better students are still attracted to a very interesting, if strenuous, life in the practice of Medicine.

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6-10, 1940, Cleveland, Ohio.

Graduate teaching and training in the specialties of Ophthalmology and Otolaryngology in our American institutions are today of the highest caliber. The American Boards for Ophthalmology and Otolaryngology have done fine work in raising the standards of our specialties. One part of their work remains unfinished, and that is educating the laity to demand that all specialists be certified by Examining Boards before being authorized to practice their specialties. Today we have in America the best possible training for the Ophthalmologist and the Otolaryngologist. With Europe in such a disrupted condition, it falls upon the American Ophthalmologists and Otolaryngologists to carry on the research problems in these fields.

Lately much has been said on the subject of socialized Medicine. It has been stated that one-third of the people of the United States is not receiving proper medical care. This statement is not statistically true. The American Medical Association has gathered figures which prove that very few, if any, who really seek medical care are denied it.

Government control of Medicine would bring forth further taxation and regimentation. We as doctors must mold public opinion to recognition of the fact that in the matter of health and disease, political or governmental supervision must not be allowed to supersede medical science. We of the medical profession believe it would be unwise to accept any form of regimentation. We must have confidence in our Mother society, the American Medical Association, and in our State and local societies that they will do what is best for both our profession and the public.

Twenty years ago it was difficult to persuade individuals to be hospitalized. Nowadays it is difficult to keep them out of the hospitals. This is due to the well-working hospital insurance plans. Group hospitalization service is becoming more popular every year. If such hospitalization service continues to increase, very shortly the problem of enlarging our hospitals or erecting new hospitals will arise. Where is the money to come from? With higher taxes and lower incomes, money given to community funds and to subscriptions for hospitals will be less in amount. Will it cause the government to take on another function — the building and management of hospitals?

If we should have an epidemic, our present hospital facilities would be woefully lacking to care for the increased load. The government is considering spending millions of dollars to build many small hospitals in the smaller communities. A survey has shown that only two per cent of the population are more than thirty miles distant from a hospital. Would it not be better to establish ambulance stations to transfer these patients and the patients from small communities to a large hospital? These patients in a large hospital would receive more skilled medical attention, the physical equipment of the large hospital would be better, and from an economic standpoint the per capita expenditure should be less.

The type of new hospital to be built should be considered. Is it advisable to have special hospitals for Ophthalmology and Otolaryngology or should these specialties have a special wing, wards or floors set aside in a general hospital? Do we wish to remain separate and thereby lose the advantage of viewing Medicine as a whole with all its ramifications and thereby limit our view as far as general Medicine is concerned? The roles that Ophthalmology and Otolaryngology are now playing in general Medicine increase daily. It is true that the nursing care in a special hospital should be better for our kind of work than in a general hospital.

For thirty years I have been a member of the Council of your Academy. Many members do not realize that the meetings of the Council are not held in secret session, but are open to the members. In the early days of the Academy, this was not so. All of the benefits that you receive today as members have been developed by your own members in the capacity of officers, committee members, or teachers. Some years ago Doctor Allen Greenwood and I suggested to the Council that some form of intensive training, other than that of the Scientific Session alone, be given. Out of this has developed the Section on Instruction, which has merited the envious admiration of other medical societies. Because the Academy is so fine an organization, we should not become lax and rest on our oars. Doctor Benedict has coined the slogan, "A Better and Bigger Academy." To you will fall the test of ever keeping it so. The officers welcome suggestions that will help to make your Academy better and of more service to you.

I should be remiss were I not to take advantage of this opportunity to pay tribute to one who has done and is doing so much for the Academy that it has become his very life. I need not tell you that I refer to our Executive Secretary, Doctor Wherry. Many of us feel that he has given so much of himself that he has taxed his strength beyond endurance. With his keen foresight, his fine, organizing mind, his ever-striving ambition for medical progress, his genial self-effacing disposition, and his ready cooperation with his able associates and assistants, the American Academy of Ophthalmology and Otolaryngology moves onward and forward.

ENDOCRINOLOGY

ELMER L. SEVRINGHAUS, M.D.
BY INVITATION
MADISON, WISCONSIN

ADEQUATE understanding of the significance of the endocrine glands involves the realization that no one of the hormones is entirely indispensible for the maintenance of life by the human body. Although such a statement seems to contradict the well-known importance of such glands as the adrenals and pancreas, special conditions can be arranged so that life continues for some time without secretions from the structures just mentioned. There is no desire to minimize the importance of glands of internal secretion or of hormones, but their true function must be stated in terms of catalyzing or facilitating chemical processes which are going on without the hormone, even though sometimes at very low speeds. Life will go on without the normal catalysis of any one of these hormone facilitated processes, although it may be at such an altered speed that the condition must be classed as disease. In a few cases this diseased condition shortens life noticeably by secondary results. The clinical significance of the various glands of internal secretion may be examined individually in the light of these general principles.

THYROID

Thyroid function is absent in complete myxedema or cretinism, yet these conditions are consistent with years of life. The primary activity of thyroid hormone is to increase the rate of oxygen utilization, whereby the biological processes of each cell are speeded up. The difference between the speed of oxidations in a body without thyroid activity and with the benefit of the hormone in normal amounts is in the ratio of about 3 to 5. When basal metabolism is only three - fifths or 60% of normal (i.e., —40%) the action of the central nervous system is so reduced that the character of the individual is more nearly animal than human. If this condition obtains during prenatal life or infancy, the devolopmental processes are also retarded, and permanent stigmata will follow. One is tempted to say that life may not go on without thyroid, for the condition is better termed existence. The expressions of this depressed oxidative function will be apparent not alone in the brain and nerves, but in sense organ functions and inferior skin of dry, thick type, beneath which is an accumulation of abnormal tissue, i.e. myxedema. Muscle metabolism suffers, the most important example of which is the myocardial weakness which may lead to cardiac enlargement. Constipation is another expression of this same phenomenon of depressed muscular activity. The other glands of internal secretion are affected, and consequently thyroid deficiency leads to secondary disturbances of the pituitary, adrenals, gonads, and so forth.

Hyperfunction of the thyroid stimulates increased oxidation, leading to increased speed of biological processes with greater demands on nerve, muscle, gland, and skin functions. The clinical picture of thyrotoxicosis is so striking that it is easily recognized.

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

Professor of Medicine, University of Wisconsin Medical School, Madison, Wisconsin.

The diagnostic problem is not great when extreme hypo or hyperfunction are concerned. As one approaches the normal state, the difficulty increases. Progress in such clinical diagnosis has followed the development of chemical methods for studying thyroid function, which have been then applied to large numbers of healthy persons to establish the normal range of variation. Although there is still much to be desired in exactness of diagnosis of thyroid function, it is this advance toward mathematical precision which has made possible the strides in clinical management of goitre and hypothyroidism in this century. Chief among the methods is the study of basal metabolism, with chemical determinations of blood cholesterol and of bony maturity contributing important help in hypothyroid states. There is urgent need for similar adjuvant tests to supplement basal metabolic rate determinations in the diagnosis of excessive thyroid function, but none of those methods recently proposed has stood the test of wide application. Consequently clinical diagnostic acumen is still necessary in distinguishing between thyrotoxicosis and such other conditions as effort syndrome, psychoneuroses, emotional tension, or the effects of drugs.

The catalytic concept of thyroid action clarifies many questions which arise in therapy. If one is to use thyroid for relief of myxedema, it is important that the dose be raised slowly over a period of weeks or months from a low level such as 1 grain daily. This makes possible the restoration of cardiac muscle during a slowly increasing demand for circulation. If the circulatory load is increased too fast the weakened heart may be thrown into decompensation. Less easily demonstrable results of rapid increase of basal metabolism are seen in the nervous system and the digestive organs. If thyroid therapy is applied to a patient whose thyroid is not underactive, the amount of catalyst is thereby increased, basal metabolism may be raised, and clinical changes may be brought about. This does not prove the existence of thyroid hypofunction, but merely applies a potent hormone as a drug (the pharmacodynamic action of thyroxin). Used with caution for definite ends this may be good clinical practice. Thus the activity of the nervous system, the heart, the skin, the digestive organs, or of some of the other endocrine glands may be temporarily increased. Such use of thyroid over long periods of time may have unfavorable consequences, because of further readjustments in the nicely balanced systems which characterize the body. Thyroid is a potent drug, to be employed with respect and in carefully measured doses. One should always use preparations of known potency, preferably U. S. P. thyroid.

PANCREAS

The general principles illustrated by thyroid action apply in analogous ways with regard to pancreatic secretion of insulin. The function of insulin is to expedite the use of glucose as a source of fat, lactose, and so forth. Glucose is used in the absence of insulin, but the rate of this use is so greatly reduced that most tissues cannot sustain their usual types of biological activity smoothly. There is an attempt to use protein and fat as alternative sources of energy, with consequent emaciation, increased nitrogen excretion, accumulation of acetone bodies from excessive fat oxidation, and at the same time reduced functional capacity in such vital organs as brain, heart, kidney, liver and skin. Ultimately the demands are too great to be met, and the body made completely diabetic as a consequence of lack of insulin succumbs to secondary results. In experimental animals, at least, this fatal outcome can be long postponed if the pituitary, or thyroid, or adrenals are re-

moved. By such operations the total demands on the body are reduced to such an extent that life may be carried on with very slight oxidation of glucose for a much longer time. Of course there is no good reason to treat the human diabetics by inducing further deficiencies, for the availability of insulin makes restoration of glucose utilization to normal a simple clinical procedure. The responsibilities of various endocrine glands for the intensity of diabetes is becoming clarified by the discovery of these consequences of gland extirpation. The clinical impression of several types of diabetes mellitus is beginning to have a factual basis.

One of the startling results of the discovery of insulin and the exploration of glucose physiology which followed was the delineation of a new syndrome, variously called hyperinsulinism or hypoglycemia. The toxic action of an excess of injected insulin is expressed as an exaggeration of irritability in the central and peripheral nervous systems. This can be produced by rapidly decreasing the amount of glucose available for oxidation by the nervous tissue. It was soon found that hypoglycemic states occurred in non-diabetics and without the injection of insulin. The first supposition was that the pancreas was producing too much insulin. Later it has been found that such factors as liver damage or removal of adrenals or anterior pituitary may produce a hypoglycemia intense enough to cause some of the same symptoms. In other words insulin is shown to be a catalyst for the use of sugar, able to reduce the circulating level of sugar below the optimum, but insulin is not the only factor in producing such changes. From this understanding of the catalytic action of insulin spring the uses of the hormone for other than substitution therapy, as in the artificial stimulation of hunger by induced hypoglycemia, or the induction of profund and sudden chemical changes with the "shock" treatment of psychotic states.

Because the changes in blood sugar concentration have such profound symptomatic consequences, and because they occur within so short a space of time after insulin has been injected, we have become aware of the importance of knowing the rate and duration of action of the various types of insulin used. This has led to the artificial modification of insulin with protamine and zinc. The clinical management of diabetes has been vastly improved within the second decade of insulin therapy. Another very important product of these studies has been the growing appreciation that there is a definite rate of becoming effective and a limited duration of effect for each hormone. These quantitative data are no less important for understanding disease and prescribing treatment than are the recognitions of the types of biological action catalyzed by the hormone in question.

ADRENAL CORTEX

The practical indispensability of the adrenal cortical hormone appears to offer a challenge to the assertion that no one of these hormones is absolutely necessary for life. Although death soon follows bilateral adrenalectomy in animals, or destruction of the glands in the human, life may be prolonged greatly if the animal or patient is protected from various stresses, such as bacterial toxins, demands for maintaining water and salt balance under adverse situations, and having to exist too many hours without intake of carbohydrate. In other words the cortical tissue produces catalytic material which facilitates the retention of sodium in the circulating fluids, of potassium in the cells, and an optimum distribution of water in the body with a consequent effective blood pressure. Furthermore, this hormone ac-

tion provides for rapid conversion of protein fragments into glucose whenever there is need for sugar to be derived from protein. In some poorly understood way, the adrenal secretion is of importance in the defense against chemical intoxicants such as are produced by many bacteria.

We are still in the process of searching for quantitative methods by which to estimate the extent of activity of these glands in the intact animal or the patient. Our diagnoses of hypofunction are still crude and limited to gross loss of function rather than small deviations from the healthy state. We are uncertain as to any condition of simple hyperfunction of the adrenal cortex. It has become possible to use preparations of adrenal gland extracts to prolong the lives, restore the health, and greatly improve the prognosis for those patients afflicted with Addison's disease, if the condition is not due to a progressive tuberculosis. There is good prospect that the exact chemical nature of the hormone molecule will soon be known. We are not yet ready to predict in what directions such hormone substances will be useful for purposes other than simple replacement. The possibilities in emergency treatment of shock from blood loss, trauma, burns, and bacterial intoxications are alluring.

One curious feature of clinical study of adrenal cortical disease has been the association of a somewhat variable syndrome with malfunction of the gland, with or without small tumors, and often with abnormal cells or adenoma formation in the anterior pituitary. This "pituitary basophilism," "Cushing's syndrome," or "adrenogenital syndrome" appears to be more a dysfunction than a hyperfunction. We stand on uncertain ground here for many reasons. The diagnoses are seldom certain without surgical or necropsy pathological examinations. Perhaps these curious cases are to be understood as examples of chemical accidents in the processes of making a highly specialized hormone molecule. The molecular structure of the adrenal cortex hormone is not known with finality but it is certainly derived from the same steroid group which includes the male and female sex hormones, and less closely related to cholesterol, vitamin D, and the digitalis bodies. It should not surprise us if slight chemical alteration in such a molecule produces bizarre results.

ADRENAL MEDULLA

The adrenal medulla receives scant attention in clinical medicine for we assume that it is not indispensable and seldom susceptible to disease. But in laboratory animals these glands may be removed without immediate death, only to be followed by profound changes in the disposition of the animals. Under a protected regime life may go on, whereas in the ordinary struggle for existence such animals soon succumb. It is probable that without adrenal medullary equipment and the associated emotional life, the human would fare poorly in his complicated life. Until we can produce methods by which to study the emotional life and the activity of the autonomic system quantitatively in the human, we shall make little progress in this field. Our attention has been diverted to the use of epinephrine as a drug with very convenient ability to cause vasoconstriction, increase blood pressure, accelerate the heart, and relax bronchial muscles. Only in the rare cases of adrenal medullary tumors with paroxysmal hypertension do we think of this gland as an endocrine offender. The surgical approach to hypertension with sympathectomy is a primitive attempt to enter this field of adrenal medulla and autonomic physiology. But our prime need is for quantitative tools to study and measure functions.

PARATHYROIDS

The interpretation of parathyroid functions continues to puzzle us in many respects. Excessive action leads to decalcification of bone and hypofunction to tetany. The simplest explanation for the data is that the secretion from the glands facilitates the renal excretion of phosphate. If this excretion lags, phosphate increases in the serum, tending to enter bone, where it is deposited as a calcium phosphate, thereby reducing serum calcium below normal, and tending ultimately to formation of excessively dense bone. If the hormone supply is above optimal levels, the renal loss of phosphate will be so great that bone phosphate will be mobilized to maintain the serum phosphate level, thereby depleting bone of calcium phosphate with cystic disease or diffuse decalcification a result. The calcium thus withdrawn from the bone raises the serum calcium level. The variations in calcium level usually studied as diagnostic criteria are thus looked upon as secondary phenomena. The clinical evidences of disturbed function, tetany, bone disease, or renal lesions wtih calcification, are probably due to the disturbances of both phosphorus and calcium levels.

Although discovery of potent extracts from the parathyroids was announced about 15 years ago, these extracts have such infrequent use in clinical medicine that no commercial laboratory has developed a well-purified hormone solution for use. Recently attention has been further diverted by the discovery that an irradiated sterol known as dihydrotachysterol, or A.T. 10, can be given orally, and will act as an effective substitute for parathyroid hormone injections. This meets a clinical emergency without solving fundamental problems.

GONADS

A constantly growing belief that the reproductive organs produce internal secretions culminated within the past 16 years in the discoveries of estrogenic, progestational, and androgenic hormones. The structural formulae have been determined and the hormones have been produced synthetically. An essential feature in the amazingly rapid unfolding of this story of sex hormones has been the procedure of bioassay by which the specific substances can be identified and the amounts present can be estimated. Of course much remains yet to be done in assay methods, as well as in the understanding of the physiology of sex endocrinology. But we know that adolescent changes are brought about by the marked increase in secretion of these hormones by ovary or testis; that the growth, maintenance, and functions of secondary sex organs are provided for through the medium of these secretions; and that the psychological characteristics of the adult as contrasted with the juvenile person are intimately dependent on an adequate endocrine activity of the gonads. The involutional processes of later decades are due in large part to the subsiding action of these same glands, as is proved by the premature precipitation of such changes in mind and body when the gonads are destroyed or removed. The explanation of these widespread effects in physiological terms is more baffling than for the other endocrine glands previously discussed. The sex hormones are powerful stimulants to growth, but this effect is exerted in a selective way on reproductive organs. It appears probable that at the same time the sex hormones inhibit other growth processes, either by means of effects on the pituitary or by expediting the union of the epiphyses on growing bones, thereby bringing to an end the growth in height of the first two decades of life. There are other interactions with non-sexual glands, including effects on the anterior pituitary which are sometimes inhibitory and again stim-

ulatory. Quantitative study of this question is urgently needed. The mutual effects of thyroid and gonads on each other are not entirely through the medium of the pituitary. One of the surprising features of sex hormone disturbances is the rarity of excessive secretion of gonad hormones — the great frequency of deficient activity. Whether this is to be explained as due to lack of capacity for greater response or to better mechanism for avoidance of excessive activity is yet to be determined. Our clinical problems are in general those of reduced activity, or often of secretion which is improperly coordinated in time and amount with the needs of optimum fertility.

A most important feature of the sex hormones is their effect on the autonomic nervous system. The purpose of this provision in terms of physiology is not yet apparent. The connections are made most evident when the climacteric occurs, marked by vasomotor and emotional phenomena of distressing type. These same symptoms may occur during adolescence, or with disturbances of these same reproductive organs during the fertile period. Of course autonomic symptoms are not always caused by sex hormone disturbance. The frequency of the connection makes this aspect of endocrine physiology of growing importance for the dermatologist, the cardiologist, the gastro-enterologist, the neuropsychiatrist, and for the rhino-laryngologist. The diagnostic and therapeutic possibilities of the sex hormone connection with the involuntary nervous system are just beginning to be understood. Perhaps all we are justified in stating at present is that an adequate supply of estrogen or of androgen tends to stability of autonomic activity, whereas a deficit is often accompanied by erratic discharges of nervous impulses leading to symptoms which produce distress.

ANTERIOR PITUITARY

All the glands described depend to a marked degree on the sustained secretion of hormones by the anterior pituitary for the integrity of structure and secretory function. In this sense the pituitary is the center of the endocrine system. The number of such anterior pituitary hormones is still undetermined; it is not necessarily as great as the number of glands affected, nor can it well be a single pituitary hormone. These effects lead to the terms thyrotropic, adrenotropic and gonadotropic hormones. One very important pituitary action is spoken of as somatotropic, for this is the influence exerted on skeleton and viscera, producing growth in size. The growth hormone stimulates protein metabolism in the direction of anabolic processes. Deficient secretion is marked by symmetrical dwarfism; excessive hormone production by gigantism or acromegaly, depending on whether it occurs before or after the union of the epiphyses. Although this hormone is apparently a protein and not yet known in chemically pure form, it has been made available in pure enough form for hypodermic administration to humans who are retarded in growth, with consequent clinical benefit and improvement in stature. This therapy must be applied before adolescent changes have gone too far to allow further gain in height. It remains for more detailed study to show the importance of this pituitary factor in the development of the orbits, the sinuses, and all the other features of the facial bones. This problem brings up at once the participation of all those features of nutrition which bear on skeletal growth and on the health of the mucosae. Systematic study of the development problems of the facial bones, with regard to identifiable factors in nutrition and endocrine action may well provide keys to the prevention of eye, ear, nose and

throat disorders which now we can only alleviate.

The most frequent disease of the pituitary is one of disturbance in function, for the diagnosis of which we are dependent on measurement of the altered function in other parts of the body. In only a few cases do we find evidences of tumor or gross anatomic lesions. Even these are to be diagnosed only by changes in the sella or in such adjacent structures as the optic tracts. If and when we can attain to methods for direct assay of pituitary hormones in blood and urine we may expect progress. All efforts in this direction to date leave us far short of routines which can be used in clinical practice.

POSTERIOR PITUITARY

The posterior portion of the pituitary gland is richly innervated from the hypothalamic centers. The secretory products of this gland stimulate the contraction of the uterus, especially the gravid or post-partum organ. Another secretion of the same tissue stimulates smooth muscle of gut or of arterioles, the pressor effect. This same hormone increases the rate of water reabsorption by the excreting kidneys. Deficiency of the pressor substance leads to diabetes insipidus, disturbing the water balance with need for greater intake to make good the loss. This hormone appears to be part of the mechanism for protecting the body against dehydration by varying the concentration of urine. Neither of these posterior pituitary hormones is essential for life, yet both are important as catalysts for processes which can proceed at slower rates without them. If hypersecretion occurs by the posterior pituitary, it has not been recognized in the clinic.

The two glands which are least dependent on the anterior pituitary, adrenal medulla and posterior pituitary, are also most dependent on innervation. The other glands will continue to function, apparently rather normally, even though denervated. We know almost nothing about the relationships between the nervous system and the anterior pituitary. Anatomically it has few nerve fibers supplying it. Yet there are many reasons for believing that impulses arising in the brain have some effects in the pituitary and its dependent glands of internal secretion. This area of investigation challenges the neurologist and psychiatrist. Of course, since the hormones circulate throughout the body and affect all types of tissue, endocrinology must interest the student in each of the fields of biology and medicine, providing him with new answers, new points of view, but most of all with new questions.

HUMAN ALLERGY AND ITS RELATION TO EXPERIMENTAL ANAPHYLAXIS AND TO IMMUNITY

J. J. Bronfenbrenner, Ph.D.
BY INVITATION
ST. LOUIS, MISSOURI

Discovery of the phenomena of hypersensitiveness occurred in the course of experiments on animals under circumstances that were wholly artificial. Indeed, analogous phenomena were never encountered in animals under the natural conditions of their environment. Thus, quite properly, the phenomena of artificially produced hypersensitiveness in animals, so-called anaphylaxis, were considered for a long time to be a mere laboratory curiosity.

However, in the last quarter of a century, thoughtful clinicians came to the conclusion that more or less closely analogous phenomena do occur in human beings and, what is particularly important, they may occur under circumstances which constitute the normal conditions of life of the species.

While the recognition of an existing state of hypersensitiveness is relatively easy when it appears as a distinct clinical entity, this recognition is more difficult in those instances where sensitivity is present as a hidden state, superimposed upon many unrelated pathological processes, or occasionally as unsuspected complicating or predisposing features of the malady. In fact, today, the state of sensitivity in man is suspected or actually recognized so frequently that routine physical examination, irrespective of the nature of the present complaint, is not considered complete unless it includes the inquiry into the so-called "allergic history" of the patient.

This wide distribution of the state of sensitivity and its frequent significance in the evolution of a variety of pathologic conditions has been aptly emphasized by W. T. Vaughan[31] in a paraphrase of the famous dictum of Fournier, "To know allergy is to know medicine." Whether it fully agrees with the view formulated by this dictum or not, your Program Committee felt that a brief review of the subject of "Allergy" as a biologic phenomenon is in order at this meeting and honored me by entrusting this task to me.

Within the limit of time at my disposal, I shall have to confine myself to a brief discussion of the question of the relationship existing between the State of Hypersensitivity and the State of Immunity, and use most of the available time to bring before you evidence to support the view that the nature and mechanisms involved in the phenomena of hypersensitivity in *man* are *identical* with those of hypersensitivity in animals, and that all the special hypotheses offered to explain the apparent differences between them are invalid.

If that is true, then this important conclusion follows: Animal experiments offer the best means to study the mechanism of allergic phenomena in man, and the fundamental facts learned by this experimental method are valid in helping to understand hypersensitiveness in man.

As a rule complex organic substances, being in colloidal state, do not readily

Presented at the Forty-Fifth Session of the American Academy of Ophthalmology and Otolaryngology, October 6-10, 1940, Cleveland, Ohio.

Department of Bacteriology and Immunology, Washington University School of Medicine, St. Louis, Missouri.

diffuse through the relatively impervious covering of the skin and mucous membranes of living animals. When taken by mouth they must be broken down by digestive ferments before they enter the lymphatics or the blood circulation. However, any break in the integrity of these natural barriers (skin, nasal, respiratory or intestinal mucosa) due to physical, chemical or biological trauma, be it accidental or wilful, may permit the passage of complex organic substances into the circulation unchanged. Such an exposure of unprotected tissues to certain of the complex foreign substances (antigens) may radically change their physiologic behavior.

This alteration is specific and consists, in final analysis, of an acquisition of alertness in the reactivity of the tissues, expressed in their increased capacity to immobilize, neutralize, and eventually to eliminate the particular foreign matter when it is reintroduced into such an altered organism. Due to the fact that frequently this more effective elimination of foreign substances resulted in the abatement of injurious effects, which these substances might have been capable of engendering, the whole change was considered to be an expression of an adaptive mechanism for the benefit of the animal and was called IMMUNITY.

However, as observations multiplied, it became evident that often this specific altered reactivity was accompanied by a considerable discomfort to the animal and occasionally even by an acute death, thus creating an impression that in such instances the preliminary exposure to the antigen not only failed to induce increased tolerance but, on the contrary, destroyed that measure of tolerance which the normal animal possessed prior to first exposure.* This paradoxical phenomenon of hypersensitiveness appearing in place of expected tolerance was given the name of "Anaphylaxis" by Portier and Richet.[25]

In order to avoid the confusion of opposing terms, "Immunity" and "Anaphylaxis," as expressing each a phase in the altered reactivity to repeated exposure to antigen, von Pirquet[24] suggested a new term, "ALLERGY," to designate the general concept of "altered capacity to react."

Thus, in its original meaning, the term "allergy" was intended to cover the totality of the fundamental alteration in the reactivity of the animal, engendered by parenteral exposure to an antigen, irrespective of the outward expressions of this altered reactivity. Elsewhere von Pirquet[23] was even more specific in stating that he proposed the term "allergy" to cover the whole range of specifically altered responses, whether they took the form of increased reactivity—hyperergy, hypersensitiveness, anaphylaxis—or were expressed in apparently diminished reactivity — hypoergy, tolerance or immunity.

Unfortunately, in spite of this explicit definition, the term "allergy" has been frequently misused, not only in the clinical literature, where it was applied as denoting phenomena which were presumably distinct from experimental anaphylaxis on the one hand, and from specific resistance on the other, but also by some of the immunologists who ascribed to von Pirquet the intent to "cover by the term 'allergy,' increased reactivity and *not* lessened."[10,11]

The specificity of the allergic response is mediated by antibodies, which thus may serve as indices of past immunogenic experience of the tissues and, if they are produced in sufficient amount to appear free in the circulation, these antibodies may be used for a passive transfer of this altered (allergic) reactivity to normal tissues.

At the Congress of Internal Medicine in 1905, F. Hamburger[16] has noted that the "specific alteration which an animal undergoes after an experimental disease is an increased sensitivity almost as frequently as it is an increased ability to resist."

Having defined the meaning of terms "allergy," "immunity" and "anaphylaxis," and having indicated their relation to each other, we can now proceed with an attempt to solve the paradox, namely: WHY IS IT that while it is generally true that presence of specific antibodies against toxins or pathogenic bacteria renders the organism relatively resistant, or "immune," to small, though effective, doses of these substances, experience has shown that under certain conditions the repeated entry of even intrinsically inoffensive antigens into a previously exposed organism now possessing antibodies may produce severe symptoms or even death?

To explain this paradox, some authors have suggested, as a working hypothesis, that the introduction of a single antigen may lead to the formation of two independent antibodies, one responsible for the heightened resistance, and the other for the heightened vulnerability. But this hypothesis has found no experimental support and has been discarded.

As a matter of fact, the accumulated evidence indicates that whenever antigen-antibody reactions occur *in vivo* there always occurs a concommitant injury to the tissues of the host, as evidenced both by local and by general symptoms. Indeed, it appears likely that the very mechanism which causes this injury to the host is also instrumental in bringing about such protective effects as warding off of an infection by immobilization of antigen by the antibody. Basically this injury consists of an inflammatory reaction which is evoked by the physico-chemical changes in the environment whenever antigen unites with antibody, and which differs from the ordinary inflammation only by its rapid onset and a relatively stormy course.

This inflammatory process is accompanied by both local and systemic symptoms closely resembling those elicited by the administration of histamine. Because of this resemblance and especially because of the highly suggestive experimental demonstration of the presence of histamine-like substances at the site of antigen-antibody union both *in vivo* and *in vitro*, the most widely-held view today is that the inflammatory reaction is actually due to the liberation of histamine-like, pharmacologically-active substances from antibody-laden tissues when they come in contact with the specific antigen.

The intensity of this inflammatory reaction varies, depending on the amount of the active substance liberated. In its more intense form, as encountered in the so-called Arthus phenomenon, this reaction consists of dilatation and stasis of capillaries and veins, edema, hemorrhage, leucocytic infiltration of the walls of the vessels, swelling and desquamation of endothelium, and thrombosis and necrosis, followed by scar formation. In most instances, however, this reaction is limited to its initial stages, that is, increase in permeability of the capillaries which permits the passage of fibrinogen from the plasma into the tissue spaces. This results in the rapid formation of a network of fibrin and of thrombi in the lymphatics located in the immediate vicinity. This in turn tends to prevent the escape of antigen from the site of entry, especially since at the same time it tends to form less mobile aggregates due to its union with antibody.

The outward expression of this injury to the host may vary in intensity, depending on the amount and nature, especially solubility, of the antigen as well as on the site and rate of its introduction into the sensitized organism.

In final analysis, the availability of antigen for a rapid combination with specific antibody determines the intensity of this injury, and if conditions per-

mit the combination to take place explosively and to involve vital structures, as the smooth musculature of the bronchioles when soluble antigen is introduced intravenously into a sensitized guinea pig, death may result before the concommitant immobilization of the antigen may become apparent. Thus, for instance, animals possessing a high concentration of antitoxin in the blood may die of anaphylaxis as a result of introduction of very small amounts of toxin intravenously, as in the experiment of Behring, 1893. Similarly, if highly immune animals, capable of withstanding many thousand lethal doses of pneumococcus intraperitoneally, receive intravenous injections of a solution of pneumococcus polysaccharide, they die with symptoms of anaphylaxis.

Since the rapidity of the union of antigen and antibody in vivo is the factor which largely determines the severity of injury, it might be expected that slowing up of the rate at which this union takes place may prevent the acute symptoms in the experimental anaphylaxis. That this is actually so can be seen in the following experiment:

While sensitized guinea pigs may be instantly killed by anaphylactic shock if a lethal dose of egg-white is injected intravenously, such animals will survive, showing only mild symptoms, if the same amount of antigen is diluted and is given very slowly, or if the total surface of antigen available for the reaction with antibody is reduced by absorption on particles of collodion.

These phenomena, called "immunity" and "anaphylaxis," are in fact merely different expressions of the same basic process of antigen-antibody union. Difference in the final outcome depends only on the extent and speed of this union and consequent intensity of the injury to the host.

In the case of an ordinary exposure to a very small amount of antigen, as in repeated exposure to infection, the allergic tissues exhibit an inflammatory response which tends to immobilize the antigen at the site of entry. This allergic response is the mechanism by which the progress of invasion is arrested and we think of it as an expression of immunity, quite disregarding the incidental local, and often also mild general, signs of injury to the host; as, for instance, in cases of mild indisposition, fever, and malaise, which may signify abortive infections in immune individuals during epidemics.

On the other hand, when intrinsically bland antigens, like egg white or horse serum, are introduced into the immune tissues, since their immobilization at the site of entry is valueless from the teleologic viewpoint (because these antigens are intrinsically harmless), all we observe on their repeated introduction is the local inflammatory reaction alone, or if the amount is large, also a general reaction, and the whole phenomenon is viewed as purely harmful (anaphylaxis).

It is clear that classical anaphylaxis as observed in animals, and occasionally in man, is a laboratory artifact which occurs only through wilful introduction of relatively large amounts of soluble antigens directly into the blood stream of sensitized animals, as in serum therapy.

Under natural conditions of exposure, antigens enter tissues of allergic animals and of human beings much more slowly and in extremely small amounts and, consequently, their union with antibodies is less explosive and the injury to the host is much milder. The actual symptoms which are thus elicited vary in form depending on the portal of entry and the amount of antigen on one hand, and on the relative local sensi-

tivity of exposed structures, but the basic mechanism underlying all these reactions is identical with that which is responsible for the explosive experimental anaphylaxis. Stated otherwise, when the allergic response occurs following the entrance of toxic or invasive antigens and minimizes their potential harmful effect, the total result appears to be protective, provided that inevitable incidental injury to the host is not too severe. However, the same reaction, if it occurs in response to an inoffensive antigen, is viewed as harmful, as the only effect observed is that of injury to the host.

This "double standard" as applied to the evaluation of allergic phenomena perhaps may be illustrated by a simple analogy of the burning of wood in a hearth. So long as fire is kept within the confines of the fire box and gives us a pleasant sight and comfortable warmth, we consider the whole process as desirable or beneficial, quite disregarding the fact that the loss of fire wood is inseparably associated with it. However, when through an accident the fire gets out of control and consumes the entire building, we consider the event as destructive, although the flame and warmth were generated here just as before.[6]

It is clear that at the basis of both of these events is a single physical phenomenon of oxidation of combustible material, the difference being only in our teleologic evaluation of the observed phenomena.

In the preceding discussion the terms "Allergy" and "Allergic State" were used as originally intended by von Pirquet,[23,24] namely, to denote the *total specific change in reactivity* engendered by an exposure to an antigen. We have stated, however, that in subsequent references to the phenomena of hypersensitiveness, many authors have used the term "allergy" in a more restricted sense, to denote the many forms of hypersensitiveness *in man only*, reserving the term anaphylaxis for the phenomena of hypersensitiveness in animals exclusively. According to these authorities, this distinction was not purely formal but was called for because of the many differences, some of which appeared to them quite important and indeed even fundamental.

Such, for instance, is the assertion that phenomena of hypersensitiveness in many may be elicited *without previous exposure* to offending substances, and indeed to many substances that are *not even antigenic in nature*, while anaphylaxis in animals can be elicited *only by antigenic* substances and *exclusively* as a result of previous wilful parenteral exposure to the antigen in question. Indeed, according to some investigators, human beings, in contrast to laboratory animals, do not readily become sensitized through parenteral exposure to antigens, and in many instances when hypersensitiveness is found to exist, it is claimed that it is determined by inheritance and that the actual mechanism responsible for the specificity is not known, but presumably is *not* due to ordinary specific antibody. For these reasons a special name "ATOPY" was coined to denote this type of unexplained human hypersensitiveness.

The notion that specific hypersensitiveness may exist *without previous exposure*, no matter how unlikely, cannot be dogmatically denied. However, before its occurrence is asserted, incontrovertible examples of its existence should be produced.

It would seem that since parenteral exposures may occur under a great variety of circumstances, all one might be justified in claiming is that in certain instances sensitivity may exist without KNOWN exposure. However, such sensitization, without the knowledge of

the victim, may occur even before birth (in utero). For instance, any anatomic imperfection or temporary injury to the placenta may permit any antigens in the mother's blood to enter the foetal circulation. This can occur not only in man, but also has been shown to occur in animals. Furthermore, presence of bile in the blood, as in cases of icterus during pregnancy, may facilitate active sensitization of the foetus, as shown experimentally in guinea pigs by Nattan-Larrier.[21] Pregnant guinea pigs receiving 0.5 mg. of sodium taurocholate intravenously, followed by horse serum within 15 hours, gave birth to young *actively* sensitized to horse serum. According to the same author, who also quotes Ratner, egg white is particularly likely to pass through the placenta at all times and in some instances presence of egg white in the circulation may facilitate the passage of other antigens as well.

Active sensitization of an infant may occur by ingestion of antigens present in the milk of a nursing mother, as recorded in the case described by Sterling and Fishman,[29] for instance. A patient received pollen therapy during pregnancy and continued to receive it postpartum. Following the third postpartum injection, the *breast fed* baby began to have paroxysms of sneezing and wheezing, which regressed when mother's treatment dosage was decreased. Mother's milk gave a skin test when injected into a ragweed sensitive individual, thus confirming the presence of free antigen in it.

Active sensitization by mouth may occur as a result of a temporary deficiency in pancreatic enzyme, deficiency of vitamins A or C, over-feeding in babies as well as in experimental animals, and especially of aspiration of food, particularly of milk in bottle-fed babies. Furthermore, sensitization may occur by a parenteral route. While this type of sensitization may occur under circumstances which permit exact record of the time and the nature of exposure, as in the case of serum therapy, in many cases parenteral sensitization may take place under circumstances which are very difficult to establish. For instance, such active sensitization may result from transfusion of blood which happens to contain free antigens; it may occur in the recipient from injection of minute amounts of antigens in the course of carrying out a Prausnitz-Küstner test, or indeed from routine skin testing for diagnosis of allergic states. Again sensitization may occur as a result of surgical procedures which leave the denuded tissues unprotected from contact with antigens present in the environment as, for instance, following tonsillectomy, adenoidectomy or resection for correction of strabismus; it may occur even as a result of percutaneous absorption as in the case of occupational dermatoses or sensitization to poison ivy. These and other antigens apparently may penetrate through the skin without any pre-existing injury, as has been so clearly demonstrated by Walzer.[33]

These are only a few of the many examples of exposure which may sensitize without the knowledge of the victim as to when and how sensitization may have occurred.

That a certain degree of correlation may be shown to exist between the hereditary pattern of an individual and the existence of clinical evidence of sensitivity is apparently supported by statistics. However, it is more likely that what is inherited is *not* the sensitivity itself (without the previous exposure to antigen — "immacuately conceived sensitivity"), but rather the "ease," or the "readiness," with which tissues of one individual respond to antigenic stimulation of a given intensity as compared with those of another. For instance, when a group of children receive injections of TA for active protection or a

prophylactic dose of antitoxin for passive protection against diphtheria, not all of them will respond with the development of hypersensitiveness to horse serum. This difference, it seems, is determined by an obscure mechanism which seems to be inherited. However, differences of this sort are not limited to man; they occur also in animals as daily experience with experimental antibody production in laboratory animals will show. Some rabbits produce copious antibody; others little. Furthermore, different species of animals differ markedly in their capacity to become sensitized by a given antigen. Thus, a single injection of egg white will sensitize guinea pigs, while rabbits require 3-5, and monkeys are feebly sensitized even by a large series of injections. Moreover, occasionally the capacity to produce antibodies to *one* antigen may be genetically linked to failure to react to another, as has been shown by Gowen and Schott[15] in the case of response of mice to the virus of pseudo-rabies and mouse-typhoid infection, respectively.

The claim that human beings, in contrast to animals, fail to become sensitized following artificial exposure to antigen is not supported by actual facts. It is well known, for instance, that serum sickness occurs in 90 per cent of all individuals receiving therapeutic amounts of serum, though the frequency of sensitization decreases as the amount injected is diminished. But even when extremely small amounts of antigens are introduced, sensitization has been shown to result as, for instance, in cases of persons offering themselves as recipients for passive transfer test of Prausnitz-Küstner[30] in cases of sensitization by the minute amounts of horse serum present in toxin-antitoxin mixtures[17] or sensitization by the traces of rabbit protein present in suspensions of bacteria that had been grown on rabbit-blood-agar.[19]

The notion that human beings fail to respond to parenteral introduction of antigens has its origin in a few observations such as that concerning the failure of repeated injections of pollen in the form of solution prepared for skin tests to cause either the production of antibody or the establishment of allergic sensitivity in normal individuals.[7] However, if one realizes that a hapten may elicit allergic response without being capable of engendering immunogenic response in a normal animal, this discrepancy disappears. At any rate, properly prepared, ground, whole, ragweed pollen is antigenic as shown in rabbits,[12] and does undoubtedly sensitize man.

These few examples show beyond doubt that human beings not only do become sensitized by parenteral exposure, but may do so in response to accidental or wilful introduction of extremely minute amounts of antigen. Thus the claims concerning the existence of a fundamental difference in the genesis of an allergic state as between man and lower animals seem to fall down in every particular.

Countless opportunities of parenteral exposure to antigen in man exist beginning with intra-uterine stage in his development and throughout lifetime, though often under circumstances that do not permit accurate establishment of the date and mode of such an exposure in any particular case.

When so exposed, some individuals respond more easily to such immunogenic stimulus than others and, as also is the case in animals, these individual differences in reactivity seem to be determined by inheritance, but they exist only as a potentiality and do not manifest themselves until the individual is exposed to antigen by some parenteral route, exactly as in the case of lower animals. As a matter of fact, while only relatively small proportions (10-15 per

cent) of the general population exhibit clinical symptoms of hypersensitiveness, a much larger proportion gives skin tests to a variety of antigens. Data collected by Walzer[34] by means of the reverse Prausnitz-Küster test, indicate that nearly 90 per cent of the general population may be absorbing traces of unchanged antigens from the intestinal tract and thus, far from denying frequency of potential exposure, one should rather wonder why is it that the clinical sensitivity does not occur more often?

While there seems to be no valid evidence to support the existence of an alleged fundamental difference in the mechanism of the establishment of the state of hypersensitivity in man, as compared with animals, before dismissing the problem let us consider the validity of other alleged differences which are stressed as bases for considering allergy in man as distinct from anaphylaxis to animals. Several such differences have been cited:

1. Symptoms of hypersensitiveness in animals are constant in each animal species, but human allergy presents itself in a great variety of clinical manifestations.
2. Sensitivity in animals is limited to one antigen, or at least to such antigens as have been *wilfully introduced;* while in man, multiple sensitivity is the rule, and frequently the offending substance is not antigenic in nature.
3. While hypersensitiveness in animals is definitely mediated by specific antibodies, in man specific sensitivity may exist without demonstrable antibody.
4. As a consequence of the preceding, the state of sensitiveness can always be passively transferred in animals, but attempts of passive transfer from hypersensitive human beings often fail.
5. While animals can be regularly desensitized by a relatively simple procedure, desensitization in man is generally very difficult to attain.

As to differences in symptomatology, it must be realized that while the systematic allergic response exhibits certain basic features common to all animals, such as fall of temperature and of blood pressure, more or less marked changes in the coagulability of the blood and increased permeability of the capillaries, many other features of this response are exhibited to a different extent and sometimes not at all in the different species. These differences in the presenting symptoms are due primarily to anatomical and physiological peculiarities of the species in which the reaction takes place. Thus, the response to systemic introducton of horse serum results in a distinctly different clinical picture, respectively, in a previously exposed guinea pig, rabbit, dog, and man.

At least some of the differences have been tentatively explained on the basis of the peculiarites of distribution of smooth musculature in the various animal species (Wells).[36] Thus, in the guinea pig, the bronchioles consist almost entirely of muscular tubes, while in the rabbit the pulmonary arteries present analogous muscular development and in the dog the walls of the hepatic veins are particularly well supplied with smooth musculature. In man, there is a great difference in the character of the response of individuals, and it has been suggested that familial distribution of the asthmatic type of response may indicate the heritable peculiarities of the bronchial tree, perhaps with respect to the distribution of smooth musculature.[8,18] At any rate, this peculiarity is not limited to man, as among rabbits; also, some animals exhibit the typical guinea pig type of reaction instead of that characterstic to rabbits on intravenous injection of antigen. Because the

nervous system of a guinea pig lacks a vomiting center, it never exhibits the symptom of retching, while this symptom is frequent in man and almost a constant characteristic of anaphylaxis in the dog.

The skin response to contact with offending antigen may be different not only as between animals of different species, but as between several locations on the body of any one animal, as well as man, and is due to differences in texture and degree of irritability of the skin. In rats, it is difficult to elicit any symptoms of anaphylactic nature, but following an adrenalectomy or after a prolonged feeding on bread and water, which causes retrogressive changes in the adrenals, anaphylactic shock can be demonstrated in these animals.[28,37] Because of these anatomical differences, the reaction of hypersensitiveness assumes a characteristic picture fairly constant for each animal species and independent of the nature of the antigen.

However, in observing a great number of allergic responses in men, it was noted that they do not exhibit any symptomatology peculiar to man but, instead, some individuals react like the guinea pig, others like the rabbit, and still others like the dog. This peculiarity, however, is only apparent and does not justify the conclusion that the mechanism of the allergic response is different in man as compared to animals. In fact, these differences in symptoms in man are probably due largely to the variations in the *portal of entry* of antigens. Even in the guinea pig, an animal in whom the picture of anaphylactic response is highly constant, marked variation of symptoms may be induced at will. In fact, the reputed constancy of symptoms of anaphylaxis in the guinea pig is due exclusively to the fact that this phenomenon is usually elicited by a generally accepted procedure, consisting of preliminary sensitization by subcutaneous or intraperitoneal route, and *the test injection by vein or into the heart*. However, even a slight variation from this procedure may lead to a very marked difference in symptoms which follow the test injection. Thus if in the test injection the antigen is introduced in guinea pigs into the carotid artery, that is, directed toward the periphery, one elicits primarily the cerebral symptoms, such as loss of consciousness and tonic and clonic seizures.[27] If the antigen is introduced into the portal vein, the gallbladder and the liver are involved.

Only when the antigen is given by the *jugular vein* do the lung symptoms appear prominently to overshadow all other symptoms.

Furthermore, many symptoms of *human allergy*, not usually seen in animals, have been produced in guinea pigs by varying the routes of primary and secondary exposures:

Asthma — by inhalation of horse dander (Ratner).[26]

Abdominal colic — bloody stool — diarrhoea by feeding (Bronfenbrenner, et al).[3]

Urticaria — in a rabbit (Auer)[1] and in a horse (Gerlach).[14]

Contact dermatitis to picryl chloride (Landsteiner[20]—by sensitizing with antigen plus dead tubercle bacilli in oil intraperitoneally).

Similarly in men, variations in symptoms observed are largely due to differences in the manner in which the primary and/or the secondary contact between the incitant and the tissues is established. If it is by the skin, cutaneous symptoms predominate; if by inhalation, respiratory; and if by ingestion, intestinal symptoms are the most outstanding single symptom, just as in animals except for the accompanying subjective symptoms, such as nausea, headache, abdominal pain, burning sensation in the

mouth, itching, and pain in the joints, which we have no means of recording in the case of experimental animals, but which undoubtedly have their counterpart. It is thus clear that variations in symptoms which are usually observed in man do not constitute sufficient basis for claiming any fundamental difference in the mechanism of the response, but are simply due to anatomical species differences and to circumstances which determine the route of exposure in man and animal, respectively.

As to the question of the relatively narrow limits of sensitivity in animals as compared with man, here again circumstances usually responsible for the establishment of the sensitivity seem to be the determining factor.

Since for sensitization to occur at all, it is necessary to have some sort of a break in the barriers to the contact with inner tissues, it is evident that when a person is so exposed and is sensitized to one antigen, he is just as likely to be exposed to many unrelated antigens within reach of the break. It is for this reason that multiple senstivity is elicited particularly frequently in connection with allergy to foods or inhalants. Moreover, some antigens may even facilitate the penetration of others. Thus milk does not easily penetrate, while egg white does. If milk is given with eggs, sensitization to both is acquired and frequently double sensitization of the foetus in utero occurs in this manner.[21]

In animals, on the other hand, we produce the break by means of a syringe which contains the particular antigen only. But if the syringe is filled with a mixture or if we should produce a break in the barriers in some other manner so as to expose the animal to contact with a variety of antigens, multiple sensitivity would undoubtedly result.

Moreover, multiple sensitivity may result also from the existence of a common antigenic component in several nonrelated complex substances. Thus Forssman antigen is present in sheep cells, in horse serum, in guinea pig tissues and in many mutually nonrelated bacteria and plants. Furthermore, complex antigens, particularly when introduced *into* the skin, may be broken up before they can exert their immunogenic effect and as a result, the recipient may produce antibodies and become hypersensitive not against the whole original antigen, but against one or more component antigenic constituents. This phenomenon is illustrated by the difference in the type of immunity produced when suspensions of type-specific pneumococcus are injected intravenously or intracutaneously, respectively; in the first instance, immunity is type-specific (directed toward type-specific polysaccharides); while in the second, antibodies are species-specific, only (reacting with species-specific protein). It is thus that an individual may react by intracutaneous test to substances to which he has never been exposed as such, but which may have come in as a part of more complex antigens.

Human sensitivity is most frequently acquired through the digestive tract and, therefore, is frequently multiple. The reason that this type of sensitization does not occur in animals is that their intestinal mucosa is usually tougher (less permeable), and their food is solid. If guinea pigs are placed on a diet deficient in vitamin C, or if they are fed large amounts of soluble protein-containing foods, such as milk and egg whites, a certain percentage of animals become sensitized.[5]

Similarly, lack of exposure is also responsible for the absence of sensitization in animals to non-antigenic substances (drugs). It has been shown, however, that by means of proper methods of exposure, guinea pigs may be sensitized to drugs. In general, it has been found necessary to secure retention of the

chemicals, either by giving them intracutaneously or in combination with colloidal carriers (Schlepper-Substanzen).

Recently Landsteiner[20] even succeeded in eliciting *contact skin reactivity* in guinea pigs sensitized by intraperitoneal injection of picryl chloride, in conjunction with dead tubercle bacilli suspended in oil.

Thus, the occurrence of multiple sensitivity and of sensitivity to non-antigenic substances is not peculiar to man, but is lacking in animals under normal conditions because of lack of opportunity for exposure under the circumstances of their natural existence.

As for the claim that specific sensitivity in man is determined by "reagins" and not by ordinary antibodies, it is due to misunderstanding.

The fact that in many instances of localized sensitivity in man, free (circulating) antibody could not be demonstrated in the early attempts, with the methods then available, has caused a great deal of confusion. Whatever may be the nature of the process or the primary site of production of antibodies, it has been shown repeatedly that they become demonstrable in some tissues sooner and more abundantly than in others and that usually the tissues more directly exposed are the first to show the presence of antibodies. It is thus that a positive Wassermann test may be obtained by examining the fluid expressed from the primary lesion a few days before the presence of any reacting substance may be detected in the blood serum.

As early as 1905, Wassermann and Citron[35] have indicated that route of introduction of antigen played a part in determining the antibody concentration in different tissues. Thus, when antigen was introduced intravenously, the antibody reached its highest concentration in the blood, but when antigen was introduced intrapleurally or intraperitoneally, the antibody reached its highest concentration in the respective cavities first. More recently the participation of local tissues has been demonstrated even more clearly. Thus Cannon[9] showed that when antigen is introduced intracutaneously, glycerine extracts of the involved areas of the skin show presence of antibody before it can be demonstrated elsewhere. Similarly when nasal mucosa is exposed to antigenic stimulus, the antibody reaches its highest concentration locally.[32]

However, if enough time is allowed to pass, or especially if exposure to antigen is repeated, eventually all structures receive either the antibody, as such, or the antigen which then causes generalized distribution of antibody.*

This delay in the appearance of circulating antibodies following local sensitization of the skin is not peculiar to man, but a general phenomenon observed in animals as well. When guinea pigs are sensitized by intracutaneous injection and are tested by the skin daily, it is found that at first they respond by a delayed reaction (24 hours), and at this time no circulating antibody is demonstrable. Later they begin to react by immediate (wheal and erythema) reaction, and antibodies are present at this time.

Another reason for the possible occurrence of allergic skin sensitivity in the absence of demonstrable antibodies in the blood is the difference in the rate of elimination of antibody. It has been clearly shown by Freund[13] that with the cessation of antigenic stimulation, the antibody disappears from the circulation more quickly than it does from the tissues. According to these studies, the uterine muscle and the skin retain the residual antibody and sensitivity to anti-

* The only exception is the fluid of the anterior chamber of the eye and the spinal fluid into which neither the antigen nor the antibody penetrate from the circulation unless inflammation of the barrier exists.

gen even longer than any other tissues. It is thus that the skin may still react to antigen at a time when systemic sensitivity no longer exists.[22] Hence, the failure to demonstrate circulating antibody does not indicate that sensitivity is due to a "reagin" as distinct from ordinary antibody.

There remains still another phenomenon which is stressed as a basis for considering clinical allergy as being distinct from anaphylaxis in animals, namely, the differences in the *effectiveness* of *desensitization*.

As stated before, typical anaphylaxis in animals occurs only under artificial circumstances, when relatively large doses of antigen are wilfully introduced at a rapid rate into the circulation of sensitized animals. However, if instead, these animals receive a small dose of antigen or if a large dose is given in high dilution and injected *slowly*, acute anaphylaxis does *not* occur although the animals may show symptoms of varying severity. Moreover, such animals may *now* withstand the rapid injection of several times the dose of antigen which would have certainly killed them if it were so given in the first place.[2,4]

This state of refractoriness, or the state of antianaphylaxis, has been erroneously called also "desensitization." In fact, the refractory animal has lost none, or very little, of its sensitivity. It will still respond specifically to antigen, provided a sufficient amount of the latter is injected. Moreover, the state of this relative refractoriness is only temporary. Depending on how severe was the response to the treatment which had for its purpose to induce refractoriness, it may last for a period of from a few hours to a few days only.

In order to produce marked refractoriness, it is necessary to subject the animal to injection of antigen in so large an amount as to cause the appearance of symptoms of acute anaphylaxis just short of death. This is what we actually do when we attempt to make guinea pigs antianaphylactic (to "desensitize" them).

In man, desensitization is less effective because in carrying it out, we are not applying what we have learned about desensitization in guinea pigs, namely, we are not injecting doses of antigen which would cause severe symptoms and would certainly be followed by a relatively prolonged and solid refractoriness. Instead, we are careful, and, of course, we should be, to inject such small doses of antigen as are certain not to produce marked symptoms and by carefully graded repeated injections, we gradually increase the solidity and the duration of the refractory period.

It is quite evident that the difference is not in the mechanism involved but in the method by which the desensitization is carried out due to our reluctance to subject patients to the procedure which would secure solid refractoriness just as promptly as in guinea pigs, but would be attended by the danger of causing anaphylactic death.

In this somewhat lengthy discussion, I have tried to show that presumably different phenomena, referred to by the names of "immunity," "allergy," "atopy," and "anaphylaxis" are in fact identical in so far as the underlying mechanism is concerned.

The apparent differences which have been stressed are not fundamental, but are the effects of the secondary factors contributed by the environment in which the specific union between antibody and antigen takes place.

While the use of these different terms is confusing, it would not cause serious difficulty if it were definitely to be understood that they do not carry any implication as to differences in basic mechanism involved. However, the unnec-

essary confusion could be eliminated entirely if all these phenomena were referred to as being the expression of "specifically altered reactivity" or "ALLERGY," employing the latter term in the broad sense which its originator intended for it.

REFERENCES

1. Auer, J.: J. Exp. M., Balt., 1920, 32:427-444.
2. Besredka, A.: Compt. rend. Soc. Biol., 1908, 65:479.
3. Bronfenbrenner. J., Hetler, D. M., Love, M., and Burnett, J.M.: J. Allergy, July, 1940, 11:466-474.
4. Besredka, A., and Bronfenbrenner, J.: Compt. rend. Soc. Biol., 1911, 71:70.
5. Bronfenbrenner, J., Hetler, D. M., Love, M., and Burnett, J. M.: J. Allergy. July, 1940. 11:466-474.
6. Bronfenbrenner, J.: Amer. Rev. TBC. Sept., 1937. 36:293-302.
7. Brunner, M.: J. Allergy. May, 1932. 3:521-522.
8. Bullowa, J. G. M., and Jacobi, M.: Arch. Int. Med. Aug., 1930. 46:306-315.
9. Cannon, P. R., and Sullivan, F. L.: Proc. Soc. Exp. Biol. and Med. Feb., 1932. 29:517-520.
10. Coca, A. F.: *Asthma, Hay Fever, in Theory and Practice:* Part I, II, and III. Thomas, 1931. Pp. 3-4.
11. Coca, A. F.: Bulletin N. Y. Acad. Med. March, 1929. 5:223-231.
12. Eagle, H., Arbesman, C. E., and Winkenwerder, W. L.: J. Immunol, Baltimore. May, 1939. 36:425-434.
13. Freund, J.: J. Immunol, Baltimore. 1927. 14:101-106.
14. Gerlach, F.: Ztschr. f. Immunitatsforsch, 1922, 34:75-94.
15. Gowan, J. W., and Schott, R. G.: Amer. J. Hyg., November, 1933, 18:674-687.
16. Hamburger, F.: Wien. Klin. Wchnschr., 1905, 18:1-3.
17. Hooker, S. B.: J. Immunol., Baltimore, 1924. 2:7-16.
18. Huber, H. L., and Koessler, K. K.: Arch. Int. Med., 1922, 30:687-760.
19. Jones, D., and Mote, John R.: J. Allergy, Jan., 1935, 6:196-200.
20. Landsteiner, K., and Chase, M. W.: J. Exp. Med. Feb., 1940. 71:237-245.
21. Nattan-Larrier, L.: Revue d'immunol. 1935. 1:468-470.
22. Park, W. H.: J. Immunol., Baltimore. 1924. 9:17-22.
23. von Pirquet, C.: *Allergie.* Julius Springer, Berlin. 1910. P. 86.
24. von Pirquet, C.: Munchen med. Wchnschr. 1906. 30:1457.
25. Portier and Richet: Compt. rend. hebd. Soc. de Biol. Paris. 1902. 54:170-172.
26. Ratner, Bret: J. Allergy, Jan., 1939, 10: 170-174.
27. Roth, I., and Szauter, B.: Klin. Wchnschr. March 12, 1932. 11:456-459.
28. Seegal, B. C., and Khorazo, D.: Arch. Path. May, 1929. 7:827-834.
29. Sterling, A., and Fishman, A. E.: Arch. of Pediat. March, 1938. 55:172-177.
30. Tuft, L.: J. Allergy, Nov., 1934. 6:25-38.
31. Vaughan, Warren T.: *Primer of Allergy.* C. V. Mosby Co. 1939.
32. Walsh, T. E., Sullivan, F. L., and Cannon, P. R.: Proc. Soc. Exp. Biol. and Med. March, 1932. 29:675-676.
33. Walzer, A.: Arch. Derm. and Syph. April, 1940. 41:692-698.
34. Walzer, M.: J. Immunol., Baltimore. Sept., 1927. 14:143-174.
35. Wassermann, A., and Citron, J.: Zeitschr. f. Hyg. 1905. 50:331-348.
36. Wells: Chemical Aspects of Immunity. Chemical Catalog Co., Inc., 1929 (see pp. 227).
37. Wyman, L. C.: Am. J. Physiol. July, 1929. 89:356-361.

THE EXPERIMENTAL ADMINISTRATION OF SULFAPYRIDINE TO GUINEA PIGS INFECTED WITH HUMAN TUBERCLE BACILLI

FRANK R. SPENCER, M.D.
RICHARD W. WHITEHEAD, M.D.
BY INVITATION
and
GERALD J. DUFFNER, B.A.
BY INVITATION
DENVER

THE CULTURES used in these experiments were made from a human sputum isolated strain. The strain was of such virulence that 0.000,01 mg. of the moist growth would cause the death of a guinea pig in three months. The bacilli used in this work were grown on Petroff's media, and in each experiment the culture was three weeks old when used. The inoculating procedure used is the one developed and used by Corper[2] at the National Jewish Hospital for Consumptives in Denver. It is as follows: 10 mg. of the moist growth from the culture tube is carefully weighed in a centrifuge tube. This is then ground against the side of the tube, using a glass rod. While doing this, several drops of a 0.5% sodium taurcholate solution are added to facilitate the grinding of the colonies. After this is complete, the suspension is made with 0.9% Na Cl solution. Successive dilutions are then made until the desired strength is obtained.

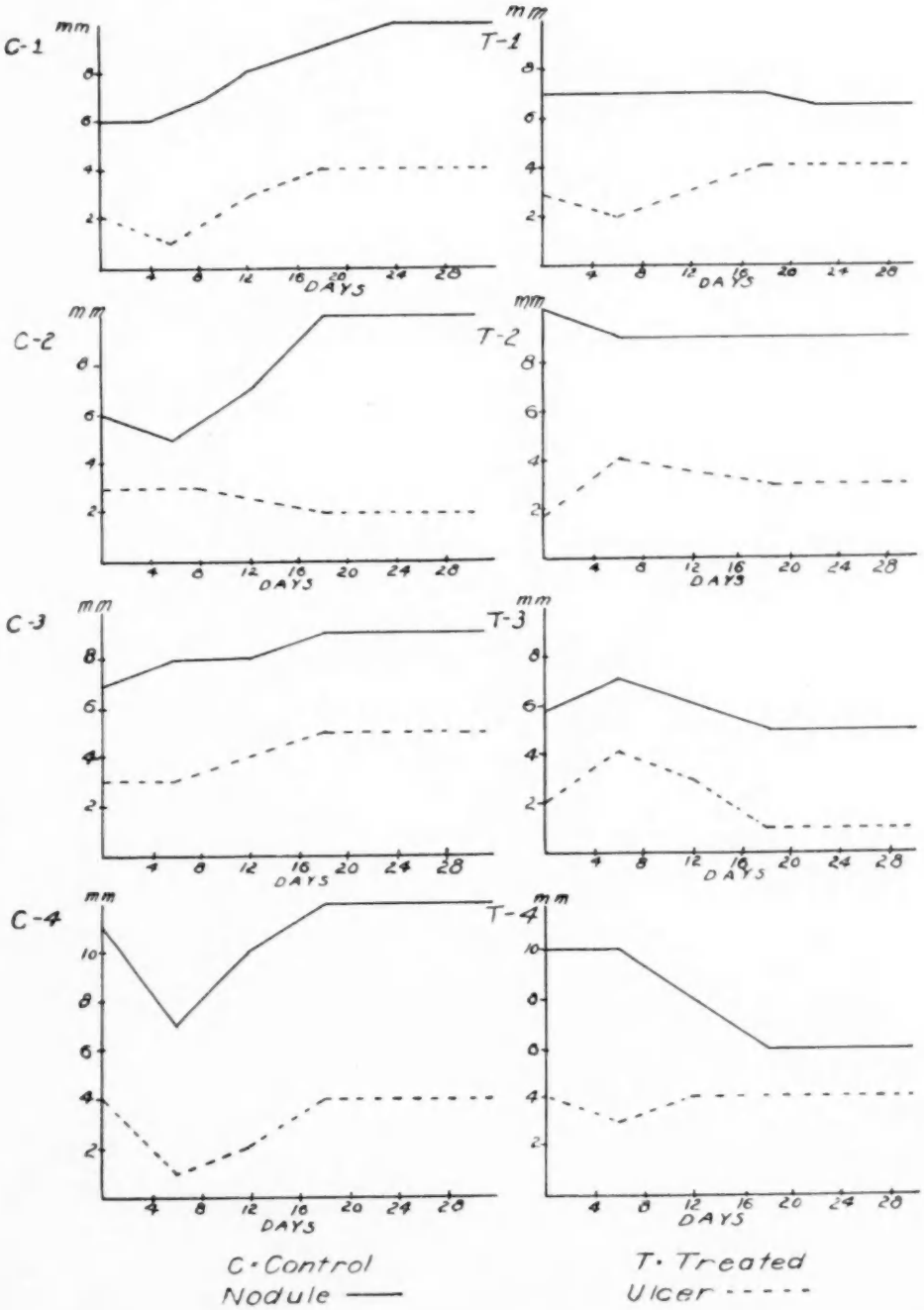
The sulfapyridine used in these experiments is the pure crystalline compound obtained from Merck and Company. The drug was administered to the animals suspended in a 20% acacia solution. The dosage used was 0.2 gm. per kg. of body weight. This dosage was decided upon because Birkhaug[1] has worked out the concentration curves in the various body tissues for this dose and found them within the range used for clinical therapy.

Guinea pigs were used for inoculation and an equal number were used as controls. The tuberculous lesions were allowed to develop before sulfapyradine was administered. The drug was withheld until the lymph nodes enlarged. The drug was first administered by a stomach tube. Later it was given in the drinking water.

Many of the animals died. These showed at autopsy an extensive tuberculosis, especially in the untreated animals. In the treated animals which survived there was slight improvement, but not enough to justify much optimism. We encountered the same difficulty which most investigators have when we tried to get a drug to penetrate a bacillus, the content of which is 40% fat. We will continue the experiments with sulfapyridine and other drugs. Sulfanilamide has been tried by other investigators and found to be of no value. We, therefore, have not used this drug. We have in mind a method of administration which may enable the drugs used to penetrate the fat laden tubercle bacillus. We hope to report better success with this later on. Chemotherapy has yielded such bril-

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

Research at the University of Colorado School of Medicine and Hospitals, Denver, Colorado.


C-1
T-1
C-2
T-2
C-3
T-3
C-4
T-4
mm
DAYS
C · Control
Nodule
T · Treated
Ulcer

liant results with the streptococcus and the pneumococcus that it seems only reasonable to expect to find a chemical which will destroy the tubercle bacillus.

Feldman and Hinshaw[3] administered sulfapyridine to guinea pigs before the pigs were inoculated with tubercle bacilli and continued the administration of the drug after inoculation. They found that sulfapyridine exerted a definite and striking modification and retardation of the expected course of the experimental tuberculosis in guinea pigs. Our experimental work so far has been confined to treatment of the guinea pigs after the tuberculous lesions have been given time to develop before any sulfapyridine was administered.

The accompanying chart shows the progress made by the controls and by the treated animals. This graph shows the average results for four controls on the left side and for four treated animals on the right side. We have used to date sixty guinea pigs. The treated animals are better than the controls, but the tuberculous lesions have not been cured as we had hoped they would be. The continuous line shows the progress of the nodule, and the broken line shows the progress of the ulcer.

REFERENCES

1. Birkhaus, Konrad E.: Proc. Soc. for Experimental Biol. and Med. Oct., 1939. 42: 270-277.
2. Corper, H. J., Damerow, A. P., and Cohn, M. L.: Amer. Rev. Tuberculosis. May, 1936. 33:701-708.
3. Feldman, W. H., and Hinshaw, H. C.: Proc. Staff Meetings, Mayo Clinic. March 15, 1939. 14:174-176.

THE STALLARD VERSUS MULTIPLE CONJUNCTIVAL SUTURES IN CATARACT EXTRACTION

LUTHER C. PETER, M.D.

PHILADELPHIA

THE REFINEMENTS of modern cataract extraction have enabled the eye surgeon to reach a ninety-five to ninety-eight percentage of good results. Outstanding in these modern advancements are (1) intracapsular extraction; (2) preservation of the pupil; (3) avertin anesthesia; and (4) corneal and conjunctival sutures. In the perfection of points (1) and (2), suturing of the corneal wound plays an important role, although the same sutures are applicable to capsulotomy extractions. In either form of operation, prolapse of the iris is a disturbing complication which can be reduced to a minimum by firm closure of the wound by sutures. Avertin anesthesia enables the operator to proceed with precision during operations on nervous and uncooperative patients; and closure of the wound by proper sutures, so far as humanly and mechanically possible, guarantees against prolapse of the iris during the convalescent period, even in patients who find it difficult to cooperate.

In my experience, although conjunctival sutures have been increased in number from a single central one to multiple sutures, prolapse of the iris occurs too frequently to consider the method of multiple sutures as perfect as it should be. It was a natural step forward, therefore, to select the Stallard corneoconjunctival suture with an episcleral bite as a more satisfactory method to accomplish the end sought. In this communication, I wish to present the advantages and disadvantages of each of these two methods, as gleaned from a sufficiently large number of cases in my practice from which to draw conclusions.

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

Professor of Ophthalmology, The Medico-Chirurgical College, Graduate School of Medicine, University of Pennsylvania, Philadelphia.

MULTIPLE CONJUNCTIVAL SUTURES

As stated previously, in my early experience one suture placed centrally seemed to be inadequate in that a prolapse to the right or left of the center was observed occasionally, with and without an iridectomy. Subsequently three, four, and five sutures were placed with better results, but not wholly as satisfactory as I felt they should be in unruly patients.

In placing these sutures it is my practice to introduce one at about ten o'clock and one at about two o'clock after the section is completed, the loops being drawn aside so as not to interfere with delivery of the lens in its capsule. After delivery, these sutures are tied, the iris is smoothed back into place, and additional sutures are introduced as indicated so as to make a complete closure. This same method was followed by Elschinig and Barraquer, each of us having adopted the technique independently of the other.

The advantages are: (1) a reduction in the incidence of prolapse of the iris; (2) prompt healing of the wound in most instances; (3) a moderate amount of astigmatism; and (4) a fair degree of security from complications if the patient shows moderate cooperation.

The disadvantages are: (1) the necessity for a deep section with danger of

the iris falling in front of the knife in some instances, thereby causing an irregular and wide iridectomy; (2) an occasional prolapse of the iris in uncooperative patients; (3) a rather high degree of astigmatism in patients who tend to squeeze; and (4) failure of the sections to hold sufficiently long in patients who fall under disadvantage (3). While the four items are rated as disadvantages, they all occur far less frequently than when sutures are omitted.

Prolapse of the iris is annoying, and, as a rule, calls for a repair operation. The deep section must be given serious consideration. A conjunctival flap hastens the healing process, and most seasoned operators endeavor to obtain a good flap. A wide iridectomy, which may follow the section, is undesirable; it should be avoided, when possible, in the interests of good end results.

A high degree of astigmatism, because of its permanency and the difficult vision which follows, is a most annoying end result after extraction. It is because of this complication, more than any other, that my attention was directed toward a corneal suture.

The Stallard Suture

Many corneal and conjunctival sutures have been offered, but that of Stallard[1] seemed to me to be the most logical, and subsequent experience confirmed my belief that it answers all the requirements for which it was proposed.

Its insertion is as follows: A small atraumatic needle, with a three-eighths curve, is used, to which is attached a 6-0 or 8-0 black silk suture. In the right eye the internal rectus muscle is grasped by fixation forceps; in the left eye fixation of the left external rectus is selected. This method of fixation prevents laceration of the conjunctiva by the usual method. The eye held firmly in this manner enables the operator to pass the corneal bite from the patient's right through the upper part of the cornea 2 mms. from the limbus for a distance of about 2.5 mms. The needle should pass through the anterior half or third of the cornea, the point of entrance and the point of exit being equally distant from the twelve o'clock meridian. The needle is now reversed in the needle holder and passed from the patient's left to his right, through the conjunctiva and through the superficial sclera for the same distance, 2.5 mms., 2 mms. above the limbus. Care is to be observed that the bite is firmly imbedded in the superficial sclera. The two sutures should be parallel and equally distant to the right and left of the twelve o'clock meridian. (See figures 1 and 2.) After the sutures have been introduced, the ends and the redundant curve of the sutures are so placed that they will not interfere with the section.

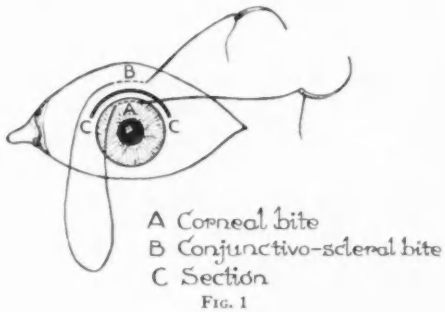
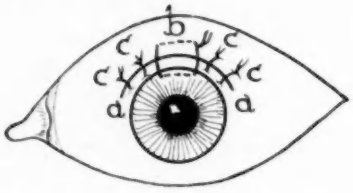


Fig. 1

The section is now made as any section should be made, with a wide sweep of the point of the knife upward as it emerges from the counter puncture and in reverse with an upward curve of the heel, so as to leave only the central section of the cornea to be severed as the knife emerges midway between the corneal and conjunctivo-scleral bites. If the section is made in this manner, it will create a small conjunctival flap on each side of the scleral bite which will admit conjunctival sutures at ten and at two o'clock when this is indicated. Reference to these sutures will be made later. If the section is large enough for intra-

capsular extraction, a little less than one-half of the cornea, the lens is delivered by the usual method, preferably with an Arruga capsule forceps and a Smith hook. If the section is not large enough, it should be enlarged with suitable scissors.



a Section
b Stallard suture
c Conjunctival sutures

FIG. 2

The suture is tied immediately after delivery of the lens by pulling the redundant silk through the conjunctivo-scleral bite (not through the corneal bite). The tie should be so firm as to make perfect coaptation of the wound. The iris is smoothened into place by an iris spatula.

If there is doubt in the mind of the operator as to the patient's postoperative cooperation, conjunctival sutures can be placed at ten and two o'clock, or where indicated, which will insure prompt healing of the wound without prolapse of the iris.

The main suture is allowed to remain for eight or ten days. Conjunctival sutures, if used, can be removed on the fifth day. The corneal suture should not be removed before the eighth day.

A back rest is in order as soon as the patient reacts from the avertin, and, as a rule, the patient can be up at the end of forty-eight hours.

The advantages are (1) prompt healing; (2) absence of prolapse of the iris; (3) a low degree of astigmatism — often as low as one diopter (this depends upon the proper placing of the suture and leaving it so placed for at least eight days); (4) little or no reaction if the lens is delivered in capsule and the cataract is not of the complicated variety; (5) a feeling of security against many complications which occur by ordinary methods of extraction; and (6) excellent visual results, if the capsule does not rupture and if pre-existing macular disturbance does not exist.

The disadvantages, few in number, arise from (1) difficulty in introducing the suture (if the eye is fixed by grasping the internal rectus of the right eye and the external rectus of the left eye, the difficulty of insertion will be minimized); (2) inaccuracy of the placing of the suture in the cornea and through the conjunctiva and episclera; and (3) failure to tie the suture firmly.

It will be observed that all the disadvantages are a matter of technique and they can be overcome by a little practice on pigs' eyes. The section offers no difficulty.

CONCLUSIONS

1. The Stallard suture, although a bit difficult to place accurately, offers a solution to some of the complications encountered in cataract extraction.
2. It enhances the value of intracapsular extraction, but is equally valuable in capsulotomy extraction.
3. It is the best safeguard to prolapse of the iris.
4. It reduces the degree of astigmatism after cataract surgery.
5. It will relieve the surgeon's mind of anticipated complications in difficult cases.
6. It is an added link in the refinements of cataract surgery which enhances the visual end results which the patient seeks, and it is a source of satisfaction to the surgeon to feel that he has given his best toward this end.

7. In my experience, the corneo-conjunctivo-episcleral suture is more satisfactory in obtaining ideal end results than multiple sutures placed only in the conjunctiva.

(Motion pictures were shown illustrating Doctor Peter's paper.)

DOCTOR PETER: The film requires no explanation. It is titled. There are two points which I feel, however, should be stressed. First, that I always use intramarginal lid sutures as a safeguard and could not be persuaded to dispense with them. Second, the movement of the knife is exaggerated in order to stress my belief as to how a section should be made.

REFERENCES

1. Stallard, H. B.: Brit. J. Ophth. May, 1938. *22*:269-273.

DISCUSSION

JOHN O. MCREYNOLDS, M.D., Dallas: We owe a very great debt of gratitude to Doctors Peter, Ellett, and Stallard for their bringing to us again an appreciation of this splendid, epoch-making work initiated by Professor Kalt of Paris, France, in 1894.

There can be no question as to the value of the methods described, and the only points to be decided relate to the details to be followed. The armamentarium is simple, consisting of a good, strong, sharp, curved needle of steel, and a piece of very small but strong thread of silk, linen or absorbable catgut.

The sutures may be confined to the superficial layers of the cornea alone, or one suture may involve the cornea while the other one involves the episcleral tissue. The corneal or limbal suture may be vertical in the meridian of 12 o'clock or it may be horizontal in the same situation. The episcleral suture may be either vertical or horizontal, but must correspond in situation to the limbo-corneal suture. As originally advocated by Professor Kalt and generally followed by others, the two sutures enter from the outside and then emerge on the outside, thus limiting the entire suturing to the superficial structures and leaving the neatly tied knot accessible when the sutures are to be removed. If one desired to preserve a conjunctival covering in addition to the corneo-scleral sutures, then the undivided conjunctival bridge may be lifted up from the sclera by special grasping forceps, thus exposing subconjunctivally the entire field of operation.

When the sutures are introduced subconjunctivally, as illustrated in the moving picture, the needles should pass out through the conjunctival bridge to facilitate the disposition of the knot. It is a safe general rule to provide that all bites, corneal, limbal, and scleral, should include practically 2 mm. of tissue in extent and ½ mm. in depth. There also should be a distance of 2 mm. between the nearest points of the inserted sutures, allowing ample space for the intervening incision. This incision may be made either with a cataract knife or with a broad angular keratome. The latter is more accurate, especially if introduced subconjunctivally. This initial incision should be short, not exceeding 10 to 12 mm., and the incision should be extended on each side to the desired extent by means of curved scissors cutting along the limbus. When the incision is completed, the iris can be dealt with according to the preference of the surgeon, and the lens delivered as usual. The corneo-scleral sutures are gently but securely tied, while the undivided bridge slips back into place, thus giving a most satisfactory conjunctival covering at the crucial points, and thus affording a double protection against iris prolapse, infection, and aggravated astigmatism.

The entire procedure can be safely, quickly, and effectively executed, leaving little to be desired for a speedy and permanent good result, if the local systemic and nervous reactions of the patient are of the normal standard.

DANIEL B. KIRBY, M.D., New York City: I agree with and compliment Doctor Peter on the presentation of his paper on the use of sutures in cataract extraction. I believe that sutures are an advance in technique and represent a safety factor in the promotion of healing of wounds, reduction of astigmatism, prevention of hemorrhage, and prolapse of the iris. I have tried all the different sutures, including the Stallard. Doctor Franklin Bracken used a similar suture for years before Stallard's publication. I agree that deep sutures, coapting the scleral edges of the limbus incision, are more efficient than conjunctival sutures, but cannot agree that the Stallard suture is the best or that it leaves nothing to be desired. Even with a deep central or vertical suture, such as the Stallard, inaccurate coaptation of edges may result and

prolapse of the iris on either side may occur. If such a suture used improperly may produce inaccurate apposition, it may be worse than none at all. I believe that three evenly spaced, interrupted radial sutures are adequate if placed in the outer third of the edges of the wound, either before the limbus incision, in the manner described by McLean, or after the limbus incision, as has been my habit. Although difficult, they may well be advised and adopted. Sutures in loose conjunctiva are hardly any better than none at all, because they do not coapt the edges of the scleral wound.

The danger of injury to the ciliary body and to the root of the iris and the possibility of devitalization of tissue must be borne in mind in the insertion of deep sutures, as should also the possibility of infection in tissues of low vitality such as the cornea and sclera, particularly in elderly individuals with low resistance to infection. In some hands and with some needles, considerable difficulty may be experienced with fixation and with passage of the needle through the dense cornea and sclera. The advantage of deep sutures and the closure of the wound far outweighs the disadvantages, but judgment must be used as they are not necessary in all cases.

In the insertion of a deep suture, such as the Stallard or Bracken, it seems logical to me that reflection of the conjunctiva from the central area above the limbus should be performed to bare the sclera for inserting the upper limb of the suture. The ends of the sutures can be passed later through the conjunctiva before tying, in order to avoid burying the knot. Passage of the needle through the relatively bulky conjunctiva may not be accurate. The tying of a suture, the points of entrance of which are 4 mm. apart (2 mm. below the limbus for one and 2 mm. above the limbus for the other as described by Doctor Peter), will buckle the tissues and cause them to invert, over-ride, or distort unless care is used in applying just the right tension for apposition. The diagonally sliced deep limbus tissue is necessarily coapted on a diagonal plane and particularly with the empty postoperative anterior chamber the edges will tend to over-ride, unless part of the suture is through the very margins or lips of the wound as in the interrupted radial sutures.

The plea for placement of sutures before the limbus section in the cataract operation is based chiefly on (1) the desire for correct apposition of the wound edges, and (2) the desire to avoid the difficulties and hazards of such manipulation on the opened eye. The argument against the preplacement of sutures is that it renders section with the knife more difficult. Insertions of the suture must be placed far enough apart to permit the surgeon accurately to pass the knife blade between them. It is a nuisance, when time has been expended on the suture, to have it rendered useless by cutting. Again, if the sutures are placed so far apart that the knife will easily avoid them, there is apt to be buckling, over-riding, and distortion upon tying the suture. The Verhoeff track suture and the McLean or Lancaster methods seem admirable for replacement. They insure accurate apposition afterwards. They are inserted in the dense corneal and scleral tissue. They go through and not over the lips of the wound, giving correct appositional closure. If in any case it seems difficult to insure a proper section without cutting the suture thread with the Graefe knife, the surgeon may use a keratome, easily inserting the point and blade between the sutures and then completing the section with scissors. The incision thus made heals well, there is no interference with the nutrition or transparency of the cornea, and there is no astigmatic aberration or other fault which may be attributed to the scissors section.

One suture may not be enough. Three interrupted sutures may seem necessary to prevent prolapse on either side of the central suture. The test for efficiency of suturing may well be the ability of the anterior chamber to hold fluid which may be pumped in under gentle pressure. I have partially filled the anterior chamber with a bubble of sterile air after tying the suture in about a dozen cases, the thought being that if air-tight, it is also water-tight. I have thought that the air, being light in weight, as compared to fluid, such as physiological saline, would tend less to carry out the iris in case of its escape. No undue reaction followed the introduction of the bubble of air.

I will tell you of my own experience and of the three interrupted sutures which have worked best. I have tried the various needles and materials which were available and have liked the cutting needles of half or three-eighths curve the best. The sclera and cornea are tough tissues, they are resistant to needle puncture, and are perforated better by cutting than by round needles. In general, a medium length needle is better than a long one. I have been satisfied with a sharp three-eighths curve needle measuring 10 mm. between tip and end with the area just behind the center flattened for the better grasp so that the needle will not turn in a good needle holder. The suture material which seems best

is 6-0 firmly braided barbless black natural silk with long fibers running away from the needle. If it is difficult to draw the suture through the tissues or if there is any tendency for the thread to bunch, the thread should be of better and smoother quality and without barbs, or should be waxed by drawing it through a mixture of two parts vaseline and three parts of white wax, finally drawing it through gauze to wipe off all excess of wax or vaseline. The insertion of the thread into the end of an atraumatic needle by pressure rather than by screw tip gives the least bulk. The doubling of the thread in the eye of any needle which requires threading increases the difficulty of pulling this end of the needle through and represents a hazard in its insertion. For the quality of sharpness, a needle must be of small calibre cutting type and of high temper. The latter feature often is accompanied by brittleness and fragility. If the sutures were deep, this would be a real danger, but in superficial suturing, as in the outer third of the lips of the cataract section, the two parts of a broken needle always can be recovered easily. However, perfect needles should not be broken. The chief cause of breaking is failure to follow the curve of the needle. We should not accept defective needles and should regularly examine our sutures, needles and instruments under magnification for defects.

(Slide.) The three interrupted sutures should be placed at 10:30, 12:00, and 1:30 o'clock on the schematic corneal clock dial or equidistant from the ends of the 2/5 to 1/2 section of the limbus circumference. The accuracy of radial insertion can be well judged by the trained eye. The chief mistake, making for inaccuracy and malposition, is the tendency to run the suture vertically instead of radially. Thus, a suture inserted in the edge of the corneal flap at 10:30 on the clock dial should not enter the scleral edge at 11 o'clock but at 10:30, and likewise the same precaution should be taken for the opposite suture. The suture at the vertical meridian at 12 o'clock is usually placed accurately for obvious reasons. The lateral sutures require shifting of body and arm position to obtain radial placement. The use of a good forceps for picking up and holding the edge of the wound is important. Such a forceps should be strong and with good teeth which will grasp the outer edge of the tissue without slipping and without undue trauma. There should be a guide between the forceps so that the blades will not buckle or turn. The needle should be passed directly to the side of the forceps so that the tissues will not turn under the insertion of the needle. A point in the technique of the use of any forceps is one that I have stressed in teaching surgical technique to residents. I had observed this particularly in Wheeler's surgery. In picking up the edge of any tissue with forceps, approach the edge of the tissue with the side of the forceps held by the fingers of the left hand as a single bladed instrument. Place the teeth of this single blade just above or below the cut edge and then bring up the teeth of the blade held by the thumb. This procedure makes for greater accuracy of placement and in many instances will do away with an intentional tremor which otherwise would be bothersome. This can be sensed better if there is a stop between the handles so that the forceps will only open to the required degree, about 4 or 5 millimeters.

(Slide.) The two lateral sutures are placed through both limbal and scleral edges, to a depth of about one-third of the thickness of the tissue, and then drawn through so that there will be a convenient short end (about . to 4 cm.). A single loose loop is made in each one before laying them aside in orderly fashion for convenient tying. The third or central vertical suture is placed in the limbus of the cornea and not immediately through the scleral edge. This suture is drawn through to half of its length and is first used for traction and elevation of the corneal flap to afford a direct view of the iris and lens capsule. Careful turning of the corneal flap does no harm in my experience. It is passed through the scleral edge and tied at the completion of the operation. It may, however, be passed completely and the lower loop used for traction on the corneal flap. It is well to make sure that the iris is not caught between the lips of the wound before the appositional sutures are drawn tight, because it is difficult to free the iris when so incarcerated. The sutures should be tied with a square knot, reinforced by a third turn in the opposite direction. The tension should be just enough to correctly appose the edge of the wound.

A word is important about the removal of sutures after healing. Fine material placed in dense tissue naturally has a tendency to cut through somewhat over a period of days. If an attempt is made to remove scleral sutures too early, there may be undue difficulty and perhaps a regrettable accident such as opening of the wound, hemorrhage, or even loss of vitreous. There is no great hazard in leaving the sutures for 10 to 12 days, particularly in nervous and sensitive patients. Then the surgeon will do well to make sure of sufficient anesthesia for the painless removal of the sutures. I have made it a prac-

tice to instil pontocaine, ½%, three drops at three minute intervals, and then with the patient recumbent, to put a few minute grains of powdered cocaine or pontocaine on the tissues near the suture.

Occasionally, a purulent infection may be observed as directly associated with the presence of deep sutures. This may be due to lack of resistance in the particular individual. If a patient has had a recent upper respiratory infection, or if positive cultures are obtained from the conjunctiva or lid margins or skin, or if the patient seems to lack vitality, it may be well to postpone the operation or operate without sutures. Needless to say, sutures should not be dragged over the skin. They should be carried from a sterile surface directly to the eye.

In conclusion, I wish to thank Doctor Peter for the opportunity to discuss his valuable paper. I agree that deep sutures are better than conjunctival sutures, and that care should be used in their placement and removal. The Stallard and Bracken types of sutures have been satisfactory to Doctor Peter and others whom I know, but I believe that direct appositional sutures, going through the lips of the incision rather than over it, are better than those which ride over the incision.

E. C. ELLETT, M.D., Memphis: Doctor Peter's paper compares the use of the Stallard suture with sutures of the conjunctiva in cataract extraction. While what I have to say may be a repetition of his own thoughts, I would like to tell my experience.

I have tried various sorts of sutures in this operation and for thirty years I have used routinely the corneo-scleral suture of Kalt. The advantages of this suture and other forms of what Colonel Wright calls "deep sutures" over sutures of the conjunctiva alone have been mentioned by many operators and my own experience tallies with that of others, to the effect that any suture which involves the cornea and sclera, especially the sclera, holds the incision more securely than one involving the conjunctiva alone. This is because the conjunctiva will stretch under slight provocation and does not offer the firm closure and support of the wound that the other type of suture affords. This applies to the Stallard suture, the Kalt suture, the McLean suture, and any others which have anchorage in the cornea and sclera.

The suture, as described by Mr. Stallard in the British Journal of Ophthalmology for May, 1938, is not exactly new nor original with Mr. Stallard. I have used exactly the same suture at times, certainly as much as twenty years ago, and again after Mr. Stallard's article appeared. I did not continue to use it because it seemed easier for me to insert the suture in the manner described by Kalt, possibly on account of my long experience with that suture. Another objection which I have found is that in cutting the Stallard suture (I use the name because it is then clear what I mean), the scissors are applied exactly in the line of the incision and on occasion, due to a movement of the patient's eye or to some fault of my own, the point of the scissors has penetrated and separated the lips of the wound. Both I and my associates have returned to the Kalt suture as being more satisfactory.

The freedom from postoperative anterior chamber hemorrhage which Mr. Stallard has enjoyed since adopting this suture has, I am sorry to say, not been my fortune. I am not sure whether or not this complication is less frequent when a suture is used, because for comparison I have no considerable series of operations without the suture. However, I see such hemorrhages with unpleasant frequency, in spite of this or any other form of suture. I believe a suture has advantages which I would not like to do without, and it gives a certain degree of safety from several complications.

Mr. Stallard leaves the suture in for fourteen days. That is much longer than it seems to me to be advisable or necessary. Sutures are foreign bodies and however inocuous and well-tolerated, one does well to remove them as soon as they have served their purpose, which I think is usually after four or five days.

JOHN M. MCLEAN, M.D., Baltimore: There was a time in the history of ophthalmology when the cataract surgeons used to argue over whether or not to use sutures; but now that that argument is practically a thing of the past, the current claim is over the type of suture. Considerable evidence is steadily accumulating to indicate the superiority of corneo-scleral sutures over any type of conjunctival flap sutures. Doctor Peter has just added further testimony along those lines.

The suture which he described has been used, I know, by a good many of those in this audience. Some of you call it a modified Kalt suture, for it is only a slight modification of the suture Kalt described at the end of the last century. Others know it as the Liegard suture, for Liegard published exactly the su-

ture twenty-five years before Stallard did, and it even reached the textbooks some twenty years ago.

Whatever name you use — Kalt, Stallard, Liegard — is of little importance. This suture is a good suture, and it is distinctly superior to any type of conjunctival flap suture; but in common with all sutures, if it dips down in the cornea, rides up over the wound, and dips down again into the sclera, it has definite faults. In the first place, your long arm, which was shown in the last slide, allows the possibility of a certain amount of lateral displacement, and in that respect fails to hold the wound in accurate apposition. Second, and I think more important, all of these sutures which go down, up, and down have this same effect if they are not tied tightly enough, and they are no better than any conjunctival suture. If they are tied a little too tightly, one can invert and spread the wound, inviting postoperative hyphemia and some other complications which we try to avoid.

In order to do away with these complications, there are several methods for placing a suture, as Doctor Kirby has suggested — through, rather than over, the lips of the wound; and as two simple little illustrations let me just show rapidly two cross-sectional diagrams of Doctor Verhoeff's well-known rethreaded suture, and the one which I described last March in the Archives of Ophthalmology. (Slide.)

ALLEN GREENWOOD, M.D., Boston: I think sometimes I should use the expression, "Lest we forget."

In 1854, Dr. H. W. Williams, then and later Professor in the Harvard Medical School, put in a suture very similar to the Stallard. Now I know all about that suture, because in 1888 I was Doctor Williams' assistant, and I have seen him put in the suture, not as far back in the sclera but in the same manner as the Stallard, but with a smaller bite in the cornea and the limbus. This was a limbus-corneal suture made in this same way. I have seen him do it a good many times, and I just want to hark back to the fact that the corneal suture isn't altogether a modern invention.

LUTHER C. PETER, M.D., Philadelphia: I desire to thank the members for their very kind discussion. It proves again that there is nothing new under the sun. Sometimes we think we have devised a new technique, but if a very careful search of the literature is made, one finds that the same technique may have been described many, many years ago.

I have no brief to file for the Stallard suture other than that it works.

A point which I would like to stress and impress upon you is that a corneo-sclero-conjunctival suture is the type of suture that is indicated. In the suture described, I have found no difficulties nor complications. Of course, there may be danger of slipping of the flap to the side if the technique is not carried out meticulously. There should be no buckling if the suture is properly tied. The knot should be placed on the sclera and not on the cornea. I have not encountered any difficulty, such as re-opening of the wound, if the knot is placed above.

One encounters no difficulty in making the section. The point of the knife should be followed carefully with the eye — a factor which was not brought out in my paper because I was dealing entirely with the Stallard suture. As the counter-puncture is made, the point is swept forward to a maximum extent. In a reverse movement, the heel is elevated so that really the section in the center to be finally severed is very small. Three movements are included in the section — first, an upward movement of the point; second, in reverse, an upward movement of the heel; and finally, the center of the section is severed. Furthermore, the knife should be brought out at right angles to the cornea so that when the suture is tied, the corneal surfaces come together perfectly.

I agree with one of the essayists in that if the suture is tied too tightly or too loosely, one may defeat the object of the suture. The proper technique can be acquired by a little practice on pigs' eyes.

I am not sure that any form of suture will prevent hyphemia — whether the suture be wholly conjunctival or whether it be corneo-sclero-conjunctival. I cannot make up my mind that the suture plays any role in preventing hyphemia. Thus far, delayed union has not occurred in my practice since I have used the Stallard suture. As a matter of fact, delayed union may occasionally occur if multiple conjunctival sutures are used, but when the Stallard suture is used, thus far I have found the anterior chamber was reformed at the first dressing, which is forty-eight hours after operation. I also heartily recommend, along with the other discussers, that a seasoned operator should acquire the technique of some form of corneo-sclero-conjunctival suture rather than depend entirely upon conjunctival sutures.

SOME EFFECTS OF COMMON INTERRUPTIONS OF BLOOD FLOW IN THE NASAL LINING

P. F. SWINDLE, PH.D.
BY INVITATION
MILWAUKEE

THE STATEMENT is heard now and then that the nasal lining is relatively avascular, but my injected and cleared specimens do not support this notion. The nasal lining is, in fact, one of the most vascular parts of the body. An extremely complex network of arteries, as that in the nasal lining,[1,2] is conducive to petechial infarction by the fragile emboli which develop in the blood stream at various parts of the body under certain conditions which have been discussed elsewhere.[3] Some of the small infarcted areas in the nasal lining may become infected and even ulcerative, but it is doubtful whether they ever give rise to the symptoms of the common cold, coryza acute rhino-sinusitis, sniffles, distemper, or whatever one may choose to call the disease. From the physiologic point of view all of these are synonymous terms, but from the bacteriologic point of view this may not be the case because the infecting agents are conceivably different in the different mammals or even in the same mammal at separate times.

A considerable portion of the nasal lining at the anterior and middle regions of the nasal passages may become inflamed and even infected without giving rise to the characteristic symptoms of coryza.

The belief is common that infection is the primary cold-inception factor. It is believed that the infection may take place in a healthy nasal lining, but that it is favored by a "lowered resistance" of the individual. Some consider that the resistance may be lowered by changing the temperature of the skin, as when one sits in a draught. According to my own observations, infection is a necessary cold-inception factor[4]; but it is the final factor instead of the primary one. It is the final one of a series of necessary factors. The factors which precede the infection work together, but in a serial order, to contribute to a state of mild pathology or a lowered resistance of a large portion of the nasal lining. The infecting agent may then take hold if it is present.

The factor which seems to be the first important one of the series is an increase in the brain volume as the result of an unusual amount of blood being forced in a short time into the cerebral vessels,[4] as when a person sits in a daught after he has led principally an indoor life in a relatively constant temperature for some time. If he has been leading an outdoor life instead and has frequently subjected his body to different temperatures the compensatory or reciprocal neuro-vascular mechanisms of the body are thereby trained and kept in training during the time so that he may sit in a draught with relative impunity. On the other hand, if he leads an indoor life for several days or a few weeks the training of the compensatory reflex neurovascular mechanisms becomes lost to such an extent that when the skin is cooled and the vessels in it constrict, the deeper vessels constrict also. One result is the increase in the brain volume as blood is rushed into the cerebral vessels. Strong inflation of the abdomen may also cause the necessary amount of

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

Marquette University School of Medicine, Department of Physiology, Milwaukee, Wisconsin.

blood to be driven into the cerebral vessels to bring about coryza if the other factors are also contributing their part.

The next factor is the decrease in the flow of blood into the nasal ramifications of the ethmoidal plexus as the result of the increase in the brain volume and a sufficient pressure of the brain tissue on the ethmoidal plexus to compress the vessels of this plexus and merely narrow their lumens. This narrowing of the lumens either does not occur or is negligible if a large opening exists in a temporal bone so that the brain can expand to a considerable extent through the opening.[4] So far as my observations go, such an opening in the skull prevents the inception of coryza. The narrowing of the lumens is negligible in the bear because the larger vessels of the ethmoidal plexus are imbedded in bone instead of being free in the cranial cavity as in other mammals.[3,4] So far as my observations go, over a period of many years, the bear does not contract coryza or distemper. The open fontanelles suffice to protect the greater number of human infants against coryza and measles for three, four, or five months. Measles is almost invariably initiated by a cold.

The next factor is the intravascular agglutination of the red cells in the static or relatively static blood in the nasal ramifications of the ethmoidal plexus. If the blood in these vessels is not already static it becomes so when the agglutination takes place, and it sometimes remains static for many hours or even a few days. The agglutinated blood may even undergo coagulation, and this complex coagulum may extend into vessels of various bones of the head and eventually cause osteomalacia or osteoporosis. Intravascular agglutination of the red cells does not occur in some animals which have been called "depressor" animals. They have been given this name because strong stimulation of a mixed nerve, such as the central stump of a sciatic, causes only the depressor effect, that is, a fall in the arterial blood pressure. The pressor effect (the rise in the arterial blood pressure), which can be obtained from other animals by stimulating the same nerve with a strong current, is due to temporary occlusion of many of the small systemic vessels by columns of agglutinated red cells.[3] These columns ordinarily break down, after several seconds, into the fragile emboli which sometimes pass through the pulmonary capillaries and cause petechial infarcts by lodging in anastomoses of complex networks of arteries,[3] as in the nasal lining. The pressor animals can contract coryza because the necessary intravascular agglutination of blood can take place in the nasal ramifications of the ethmoidal plexus. The depressor animals can live with others afflicted with coryza or distemper but not acquire the disease themselves. The intravascular agglutination conceivably fails to take place in some hemopheliacs also. At least, some of these "bleeders" do not contract coryza.

Statistical investigation reveals that people suffering with paralysis agitans or Parkinson's disease either do not contract coryza or they contract it less frequently than before the onset of the paralysis. Certain observations suggest that this is the case because the constant muscular movement in Parkinson's disease steadily uses up in some way a certain unknown agglutination factor (an X-factor). It is presumed that the depressor animals and some hemopheliacs do not have the X-factor in sufficient amounts to cause the necessary intravascular agglutination for cold inception.

The coagulum in the nasal lining eventually breaks down, and the fragments circulate as infected emboli to the lungs. Pneumonia may follow if the lung tissue in the vicinity of such an

embolus becomes pathologic enough for infection to take place.

REFERENCES

1. Swindle, P. F.: The Architecture of the Blood Vascular Networks in the Erectile and Secretory Lining of the Nasal Passages. Ann. Otol., Rhin. and Laryng. 44:913 (Dec.) 1935.
2. Swindle, P. F.: Nasal Blood Vessels Which Serve as Arteries in Some Mammals and as Veins in Some Others. Ann. Otol., Rhin. and Laryng. 46:600 (Sept.) 1937.
3. Swindle, P. F.: Occlusion of Blood Vessels by Agglutinated Red Cells, Mainly as Seen in Tadpoles and Very Young Kangaroos. Am. J. Physiol. 120:59 (Sept.) 1937.
4. Swindle, P. F.: The Architectural Arrangement of the Nasal Arteries and the Angioarchitectural Basis of the Common Cold. Tr. Am. Laryng. Rhin. and Otol. Soc. 42:309, 1936.

DISCUSSION

A. W. Proetz, M.D., St. Louis: Any discussion that I make of this very marvelous presentation must be largely an expression of admiration. Only someone as conversant with this work as Doctor Swindle himself could discuss it adequately. The first time I visited Doctor Swindle's laboratory and saw his beautiful preparations I came away with my mouth open, and it has not, in fact, closed yet.

This work is another example of many investigations by men who are not in the laryngological field, but who have contributed almost incidentally to it the things that the laryngologists want to know more than anything else. It happens so often that one listens to men in other branches recite some fact casually that we have been anxious to hear all our lives, and which has not appeared particularly significant to them.

Aside from this idea of agglutination in the production of coryza, I think one of the most important things Doctor Swindle has done is to lay before us these remarkable specimens of the circulation of the nose. We have talked pretty glibly about the nose warming the air which goes over it, humidifying it at the same time. But who has seen a more effective mechanism for radiation than these pipes, capillaries, and tubes which Doctor Swindle has just shown us? If for no other reason than this, his exhibit is of extreme importance to us. It is the basis of the physiology of the nose, which has just begun to attract our attention.

Now, Doctor Swindle's idea of agglutination, thrombosis, and embolism in these vessels of the nose is a little bit shocking, which does not mean at all that I disagree with it. It means that one certainly has not thought previously of a thing as dangerous as embolism and thrombosis taking place just as casually as this appears to do.

All of these specimens, of course, come from dead animals. In the first place, I would like to ask Doctor Swindle whether the animals died from the infections that are shown here or whether they were found incidentally on dissection; also whether the infections were severe or not. Doctor Swindle led us to believe that the condition he described occurs rather frequently, and I should like to know whether that is the case.

Of course, in animals a relatively massive coryza may be fatal, whereas in the human it isn't. I don't know what the difference may be.

I simply am not equipped to discuss the theory, because I have no personal experience with the observations upon which it is based. These two questions arise in my mind, and I hope a great many others will be asked of Doctor Swindle, because I think this is an extremely important contribution.

J. E. Mulsow, M.D., Milwaukee: This new conception of intravascular agglutination and capillary stasis of the red blood cells as demonstrated by Doctor Swindle offers a further explanation of the experiments conducted by numerous investigators with regard to the changes occurring in the nasal mucosa when an individual is subjected to sudden or prolonged temperature changes. The nasal mucosa presents one of the greatest vascular areas of the body. With these recognized experiments of these newly observed phenomena of intravascular agglutination of red blood cells and blood stasis, which is enhanced by this vascular pattern of the nasal mucosa, Doctor Swindle has offered us a view-point in considering the seriousness of the neurocirculatory effect of temperature changes. This may explain the almost trigger-like effect in the nasal mucosa by temperature changes as borne out by the experiments of Mudd and his associates, Taylor, Hines, Spiesman and Arnold, and others. Hill and Muecke (1913) found that when an individual who had been in normal physical condition was exposed to a cold atmosphere, the nasal mucosa quickly became pale owing to the constriction of the blood vessels, but the mucosa still remained thickened and swollen. Spiesman and Arnold noted that when cold water was applied over large areas of the skin, that is, the entire

back, or when the lower limbs were immersed in cold water, definite changes occurred in the nasal mucosa of young, healthy subjects. An ischemia occurred, the amount of which was definitely in relation to the size of the area of skin that was stimulated. It is possible that the findings of these investigators bear out the experiments of Doctor Swindle with regard to the agglutination of the red blood cells and blood stasis. Doctor Swindle believes that this agglutination occurs in patients with an acidosis. This may offer the rationale for alkalinization in cases of upper respiratory infection and in cases where infection is suspected in the tissues.

P. F. SWINDLE, PH.D., Milwaukee: Doctor Proetz brought out the point that the notion of intravascular agglutination is shocking. It is not quite as shocking to us at the present time as it was in the earlier years in our laboratory. We have become accustomed to it because we have seen it so many times in living animals. We have demonstrated it on various occasions. The first time was many years ago when some observations were being made on the tail of a tadpole which had its body fastened down in such a manner that it could not swim away. A microscope was trained on the tail. We could clearly see the blood vessels in it and the blood circulating in these vessels. When the tadpole flapped its tail periodically, as tadpoles seem always to do under such a condition, some interesting changes in the circulation took place. Immediately after a paroxysm of the flapping had ended, the blood vessels of the tail were dilated and the blood was static in some or all of the small vessels in the microscope field. The stasis was due to agglutinated red cells in the dilated vessels. The columns of agglutinated red cells regularly broke down twenty-five or thirty seconds after the flapping ceased. That is, de-agglutination took place. In cases, the de-agglutination was so complete that individual erythrocytes circulated away into the veins, but in other instances the de-agglutination was so incomplete that small clusters of the red cells circulated away as fragile emboli.

Again, the agglutination of red cells was observed in the vessels of some young, hairless kangaroos from the pouch. It was necessary to keep each of these little, highly transparent animals very quiet for a few minutes and then touch it or stimulate it in some other appropriate way to cause it to make a sudden, vigorous movement or a short series of vigorous movements. After a paroxysm had ceased it was observed that there was no circulation in a few or many of the small vessels, that some of the vessels were occluded by solid columns of agglutinated red cells, that at times the de-agglutination was very complete, and that it was very incomplete at other times. In the little kangaroos we were able to observe the lodging of some of the fragile emboli in some of the small systemic arteries. These emboli were undoubtedly stable enough so that they passed through the pulmonary capillaries and reached the arterial side of the systemic circulation without being destroyed on the way. We have also observed the phenomena of intravascular agglutination, complete de-agglutination, and incomplete de-agglutination in other mammals.

It seems to me at the present time, in view of some observations made by Doctor End in the Physiology Laboratory at Marquette University, that even the disease known as the bends or compressed-air illness is due to the development of the fragile emboli and their lodging and standing up in parts of the body in which the networks of arteries are most complex. It is in a complex network that a fragile embolus stands up best and most commonly causes petechial infarction. A fragile embolus would be hammered and washed to pieces if it should lodge in an endartery in the sense of Cohnheim, but not if it should lodge in a part of a complex network of arteries. The network protects the embolus by distributing and otherwise diminishing the mean blood pressure and the pulsatile variations in the individual vessels of the network sufficiently so that the tendency of the fragile embolus to be hammered and washed to pieces by the blood is not very great. It is also the case that the mean pressure may be almost the same on both sides of the lodged embolus. A fragile embolus in an artery of a complex network of arteries is also not molested much because the blood can circulate around it in many arterial channels instead of against it.

An acid medium favors the development of the fragile emboli. This was demonstrated in some of the work with the tadpoles. Also, some experimental work with mammals, including the human being, points in the same direction, and the results further indicate that a fragile embolus becomes more stable in an acid medium.

I am not certain that I know yet what the acidity is deep among the vessels of the nasal lining. It might be the case that the degree of acidity or alkalinity discussed in the preceding paper this afternoon* is confined to the more superficial part of the lining. Independ-

* "The Significance of the *p*H of nasal secretions in Situ," Noah D. Fabricant, M.D., Chicago.

ently, however, of what this acidity is under normal conditions, I entertain the ideas that the tissue becomes relatively acid when the blood stops circulating in it for a time, that the acid medium is an important factor contributing to the agglutination of the red cells of the static blood, and that this agglutination may or may not be the incipient stage of intravascular coagulation. It may be said that an area of tissue in which the blood becomes static is an incipient infarct in so far as the area becomes mildly pathologic as a consequence of the stasis. This may or may not become a full-fledged infarct.

"Is the intravascular agglutination in the nasal lining common with human beings?" I am only presuming that it takes place in the nasal lining of the human being. I believe the nasal lining of the human being is not essentially different from that of other mammals. Unfortunately, however, I have not succeeded, in recent years, in getting human specimens which were entirely appropriate for this work.

The question was raised as to whether the animals I discussed were killed or whether they died of the infections. Some of them died. Others were killed when certain stages of the disease were reached. To the best of my knowledge zoo mammals and human beings do not die of uncomplicated coryza. Such a complication or after-effect as pneumonia, nephritis or meningitis may be fatal. Some zoo mammals contract coryza as frequently or even more frequently than human beings do, some others contract it relatively infrequently, and some do not contract the disease.

Doctor Mulsow referred to some interesting work on temperature changes. I have approached some problems of temperature changes in the nasal lining and elsewhere in the body from various angles, and I shall take time to speak of a small number of observations which I believe are especially instructive.

There was a dental student in Milwaukee who had a portion of a temporal bone removed when he was eight years old. I learned about this a few years ago, in the spring of the year. In the physiology laboratory a receiving capsule of a volume recorder was placed over the opening, and then cold water was allowed to flow onto the lower arm and hand. The brain volume curve went up and staid up at a rather high level as long as the water flowed onto the arm. The arterial blood pressures, systolic and diastolic, also went up. The curve and also the arterial blood pressures fell rather abruptly when the water was turned off. He returned the next fall, as he had promised to do, so that he might act as subject for a demonstration of this brain volume curve before a class of medical students. On this occasion we got a slight fall, instead of a conspicuous rise, in the brain volume curve, and the arterial blood pressures did not change significantly. In the spring of the year, when the subject first came to the laboratory, he had been leading the somewhat sedentary, indoor life of a student, and the brain volume curve went up in response to the cold water on the arm because some reflex, reciprocal, neurovascular mechanisms were not in perfect training at the time. When he came to the laboratory the second time, however, the volume curve went down slightly (instead of up) in response to the water because he had been leading an outdoor life for a long time. He had been subjecting the skin frequently to various temperatures. The reflex, reciprocal, neurovascular mechanisms were at that time in good training, so that the deep vessels in the body underwent compensatory dilatation, instead of constriction, when a part of the skin was cooled.

The problem of temperature changes of the nasal lining is interesting for different reasons. This lining is one of the erectile tissues of the body. I do not claim that the erectile mechanism in this case is the same as that found in the liver or in the corpus cavernosum of the penis. The small postreticular endarteries in the lining may constrict, in response to cold air for instance, and dam blood back into the larger, inflatable arteries of the networks and cause the volume capacities of the arterial anastomoses to increase greatly. The lining then becomes thicker and temporarily warmer. However, tissue fluid of the lining is pressed out into the nasal passages, and some heat is lost with this fluid. Above and beyond this heat loss there is also a loss of heat by evaporation which continues to take place after liquid has ceased to seep rapidly out of the lining. Under ordinary conditions, the heat of evaporation is rapidly replaced by heat of the arterial blood which circulates rapidly into the lining, but when the lining is in a state of erection it cools down because of the heat loss which is imperfectly replaced by the slowly circulating blood in the lining.

I hope I have not omitted any important questions that were raised.

Before taking my seat I want to say that I greatly appreciate the opportunity given me to speak before this body, and also that I appreciate the opportunity given me by the Academy to exhibit the specimens which are in my booth.

DIFFERENTIAL DIAGNOSIS OF THE PHORIAS

AVERY DE H. PRANGEN, M.D.
ROCHESTER, MINNESOTA

FIRST, we may well ask, "What is normal in muscle balance?" The older I become and the more experience I have in the practice of ophthalmology, the more I ask myself this question. Before we can judge the abnormal, we must first be able to establish the normal. As in any other field of medical diagnosis, experience widens the limits of normal and narrows the limits of that which is actually pathologic. Excluding definite strabismus and obvious deviations of the eyes, I would say that any state of extraocular muscle balance which causes a person no discomfort is normal for that individual. This is, of course, a broad statement and is open to argument; yet I believe that it is relatively true. At least we are not called on to interfere in theoretic states of imbalance which are symptomless to the patient. This general theme of avoiding unnecessary interference is a cardinal point of view in the intelligent practice of medicine. Much trouble could be saved if it were more closely followed. For patients who persistently complain of asthenopia and whom ordinary corrective measures have failed to help, one should then look for the unusual. First to be carefully scrutinized in such troublesome cases is the muscle balance. Is perhaps that state of balance which we had previously judged to be normal really abnormal for this particular set of eyes? A review and restudy of the state of balance may indeed prove it to be abnormal when looked at critically with the patient's discomfort in mind. We may have passed over a frankly abnormal state of balance. Reconsideration often discloses such a state of affairs to the benefit of the patient.

In spite of the foregoing philosophy, we must have certain rules of thumb indicative of so-called normals in the diagnosis of conditions of the extraocular muscles. Certain comprehensive data must be collected concerning the position of the eyes, positive and relative, in action and at rest. Their mobility and motility must be studied. The powers of duction, or vergence, must be determined. Accommodation, refraction and vision, fusion, and stereopsis are evaluated. An attempt is made to put together this diffuse information into a composite picture telling the story of normal or abnormal in muscle balance for the set of eyes being considered. Any of these data considered separately without reference to the whole will not lead to a correct diagnosis. Separate numerical values, such as esophoria or exophoria, do not tell the whole story and may be very misleading. Muscle diagnosis consists in the weighing of one set of data against another, trying to figure out the existing relationships and their composite significance. Relationships and relative values count more in diagnosis, I feel, than the actual numerical values found.

Taking for granted that visual power for distant and near vision, together with ability to fuse, have been determined, let us consider supposed normal values for the phorias or rest positions of the eyes. It is essential that the phorias be determined both for distant vision and for near vision, so that these

Read before the American Academy of Ophthalmology and Otolaryngology, Cleveland, October 10, 1940. Section on Ophthalmology, Mayo Clinic, Rochester, Minnesota.

values can be compared. It is said that for distant vision or infinite gaze, a low degree of esophoria, 1 to 3 prism diopters, is normal. In near vision an exophoria of perhaps 5 prism diopters is regarded as normal. Why is this so? Physiologically, when the eyes look from near objects into the distance the diverging mechanism is dominant and the converging mechanism is recessive. In contrast, when the eyes change from distant vision to near objects the converging mechanism dominates and the diverging mechanism is recessive. Thus, to hold the eyes properly fixed on distant objects, divergence is taxed, and to hold fixation on near objects, convergence is taxed. It is also a physiologic law that to rest from one position of effort, the part of the body involved shifts to the opposite position. Also any given task cannot be continuously maintained without rest, even though it is momentary. Thus, if divergence actively maintains fixation in distance, the rest position for distant vision must be a converging of the visual axes (esophoria), the opposite used to maintain distance fixation. Conversely, if convergence maintains the eyes in near fixation, the rest position for near vision must be the opposite to convergence of the visual axes, or exophoria. Thus, when we break up binocular fixation, as we do when measuring phorias, we would expect in normal eyes to find esophoria in distant vision and exophoria in near vision. Physiologic esophoria in distant vision and physiologic exophoria in near vision have long been accepted.

This theme of the dominance of divergence in distant vision and the dominance of convergence in near vision has been employed by Duane and others in attempting to classify anomalies of horizontal gaze, divergence and convergence. It has been argued that since divergence controls distant vision, anomalies of divergence will appear to be more marked in distant vision. Vice versa, anomalies of convergence will be more prominent in near vision. On this basis I have prepared an outline to illustrate the diagnosis of the lateral phorias.

Deviation greater for:

I. Distance		A.		II. Near
1. Exophoria	←	Exophoria	→	1. Exophoria
a. Divergence excess				a. Convergence insufficiency
2. Esophoria		B.		2. Esophoria
a. Divergence insufficiency	←	Esophoria	→	a. Convergence excess

Therefore, we have insufficiencies (weakness) and excesses of divergence and convergence established as definite diagnostic entities. Such a scheme enables one to say without too much uncertainty that an anomaly of lateral balance is primarily one of either convergence or divergence. It is a tremendous help in narrowing down toward a more exact diagnosis of lateral imbalance. True it is that many cases do not fall exactly into this comparative rating. The longer an anomaly of either convergence or divergence exists uncorrected, the more certain is the opposing function to become secondarily involved. It is natural that, as primary excesses of the functions, divergence and convergence, persist, they will be followed by secondary weakness of the opposing function. Likewise, primary weakness of convergence and divergence will be followed with the passage of time by secondary contractures or excesses of the opposing function. In such a mixed picture where both weakness of one function and excess of the opposing function exist, further study must be carried out to dis-

tinguish between the primary and the secondary defects.

The amount of the phoria found is about equal for distant vision and near vision in mixed cases. They, therefore, cannot be distinguished from one another on the basis of the amount of phoria alone. Other findings must be turned to such as powers of rotation, powers of vergence, and the state of the accommodation. As I said earlier in this discourse, a knowledge of the phoria alone does not make a diagnosis. It is merely a portion of the necessary data. After the amount of the phoria for distant and near vision has been determined, one must consider the powers of duction, or vergence; that is, one must study the dynamic powers of convergence and divergence of the visual axes and compare the results with the rest positions of the eyes (phorias). In studying phorias we break up binocular fixation and allow the eyes to assume positions of rest, whereas in study of vergence we permit binocular fixation to exist and study its maximal power to maintain single binocular vision. This is done by determining the maximal prism power which convergence and divergence can overcome up to diplopia. This applies both for lateral and for vertical movements (vertical divergence). Lateral prism divergence is a constant measurement ranging from 5 to 8 prism diopters as normal. Lateral prism convergence is a variable measurement ranging from 0 to 50 or even more prism diopters. Some patients seem to have an aversion to overcoming prism base out, but usually with encouragement and persistence this ability can be determined. In general, it may be said that prism convergence power should be two to three times as great as prism divergence. It is the ratio of one power to the other that is more important than the actual numerical readings obtained. Vertical prism divergence power is quite constant, the normal being from 2 to 4 prism diopters. In exceptional cases there may be as much as 10 prism diopters of vertical prism divergence. Vertical divergence below 2 prism diopters is abnormally low.

When prism convergence and divergence powers have been obtained and these figures compared with the phoria data, one is usually in a position to forecast the diagnosis of lateral and vertical balance. It goes without saying, however, that the powers of rotation of the eyes in the various positions of gaze, that is, the different muscles, should be carefully examined. Definite muscular anomalies are thus spotted which have a direct bearing on the diagnosis of a phoria, either lateral or vertical. The value of the cover test in bringing out latent weakness in the various muscle fields is unquestioned, and it should be used as a routine. White has aptly stressed this, especially in the oblique fields of gaze for vertical anomalies. His use of prisms and the cover test to measure latent deviations is very useful.

In considering vertical imbalance, the possibility of the existence of double hyperphoria must be kept in mind. If double hyperphoria is present, the indiscriminate prescribing of vertical prisms, or the performance of surgical operation, is likely to aggravate the symptoms still further.

In studying convergence power, I like to observe the actual clinical convergence ability with the eyes fixing on a small object (end of pencil) and measure the convergence near point in centimeters. In this way one acquires his own ideas of the state of a given convergence mechanism. The prism convergence may be misleading but a measurement of the actual power to converge in centimeters is definite. Measured from the brow, 5 to 6 cm. is the average normal. One can take such a measurement for evaluation of conver-

gence or he can translate it into PCb (prism, convergence base line) value in prism diopters. PCb in prism diopters is equal to the meter angles (MA) of convergence multiplied by the pupillary distance in centimeters, that is, PCb = MA × PD. The meter angles of convergence are equal to the convergence near point in centimeters divided into 100. To read at 37 cm., the average reading distance, it requires 17 prism diopters PCb. The normal PCb to give adequate reserve of convergence should be at least twice this value.

Of course, the relation of convergence to accommodation should be determined. The normal values for the accommodation at the different age periods are well established (Duane), and any marked and persistent deviation from these values should be noted and allowed for in evaluating muscle imbalance. The state of vision and the refractive error should be known and should be fitted into the picture. This is also true of fusion ability.

In differential diagnosis of the phorias the problem of diplopia often is encountered. If patients complain of diplopia, the question arises whether it is attributable to phoria or to paresis or to paralysis of the extra-ocular muscles. This is sometimes difficult to decide. As a rule, there is a distinct difference between diplopia owing to phoria and diplopia owing to individual muscle weakness. Diplopia resulting from phoria is much less disturbing and incapacitating. Patients with diplopia attributable to phoria are able to keep both eyes open and to orient themselves to their environment without difficulty. On the other hand, diplopia owing to acquired paresis or paralysis of the various extra-ocular muscles is confusing and the patients tend to close or occlude the affected eye in order to shut out the false image. Also, diplopia caused by phoria is found, with a red glass, to be present and about equal in all the fields of fixation, whereas paralytic diplopia is found to be limited to the fields of action of the affected muscle or muscles. The borderline between phoria and tropia is often not clear. I prefer to limit the use of the term "phoria" to those states of imbalance in which actual, visible deviation is absent.

In the diagnosis of muscle imbalance, it is important to emphasize the factor of time. As a rule, immediate diagnosis is not essential. Repeated observations over a period of time are most useful in establishing correct diagnoses. The findings in a given case, and their diagnostic significance, often change with repeated observations.

In arriving at a diagnosis of abnormal binocular muscle balance, we must obtain by careful study and re-examination a definite series of data.

1. The powers for distant and near vision are essential.
2. The refractive error and accommodative needs are studied.
3. The eye movements in the various fields of fixation, with and without the cover test, are observed.
4. The convergence near point or PCb is taken.
5. Fusion is investigated.
6. Rest positions or phorias for distant and near vision are noted and compared.
7. Vergence powers are determined.
8. The character of any existing diplopia is studied.
9. Symptoms are evaluated and the individual is classified medically, neurologically and sociologically.
10. Repeated observations are made.

By a thoughtful assembling of these facts, it should be possible to arrive at a definite diagnosis. The scheme here offered for differential diagnosis is not exact or inflexible; it is, rather, a working basis for diagnosis.

DISCUSSION

GEORGE P. GUIBOR, M.D., Ottawa, Illinois: A normal muscle balance (which means that degree of heterophoria found in the average patient) is a variable muscle balance. The essayist emphasizes this fact, and also the fact that experience widens the limits of what is normal and narrows the limits of that which is pathologic. Hence, if we set up an ideal standard and say that orthophoria, meaning no movement of the eyes under cover, for distant vision and for near vision is normal we find every person whom we examine to possess an abnormal muscle balance. Of this observation I am certain, because I have not once seen this ideal situation after a careful analysis of the ocular motility of thousands of patients. But, the most important statement in this paper, which I wish to repeat is, "Any state of extra-ocular muscle balance which causes the patient no discomfort is normal for that person." This means, therefore, that we must judge an abnormality of motility by the symptoms of discomfort about which the patient complains, and not by the degree of ocular deviation determined by some test to dissociate fusion. Therefore, a symptomless heterophoria should not be treated. It is only when the fusion ability of such a patient is unable to cope with a moderate or marked deviation from binocular fixation and symptoms referable to the deviation arise that we can conclude that this or that heterophoria in question is abnormal.

No matter what our conception of abnormality may be, however, we must remember that a deviation also varies in the individual who possesses it. Let us take, for example, a patient who is in good physical condition and without ocular complaints, but who possesses a convergence ability less than the convergence existing in the average person. When such a patient develops influenza, diphtheria or has some chronic malady such as an anemia or hypothyroidism, the convergence efficiency is lessened and the fusion power of such a person must be used to overcome the defect in convergence. If the amplitude of fusion is not great enough, or does not develop spontaneously enough to withstand the debilitating factors present, then a true convergence defect for that person is present because such a patient will have discomfort when reading. Therefore, every patient who has ocular complaints referable to abnormal motility is entitled to a general physical check-up, which should include a basal metabolic rate determination, a complete blood count and a urinalysis. It is most surprising how such patients will improve following treatment of a general condition (anemia, and so forth) causing the temporary inability to converge comfortably.

Likewise, the muscle balance will vary depending on the test used and also on how completely one disrupts the compulsion to fusion during the tests. Doctor Prangen emphasizes these observations when he says, "Review of an apparently normal muscle balance may reveal an abnormal balance for a particular set of eyes."

Finally, we must remember that an abnormal muscle balance varies depending upon the refractive correction and upon the accommodative status at the time the test for the balance is done.

In conclusion, I believe that Doctor Prangen should be complimented for calling to our attention the following: (1) that a normal heterophoria is variable; (2) that a deviation is considered abnormal only when it produces subjective symptoms; and (3) that a muscle balance is varied by the refractive errors, the accommodative status, the direction of gaze, the convergence and divergence functions, and the fusion ability.

DISCUSSION

DERRICK VAIL, M.D., Cincinnati: At the time I graduated as ophthalmic resident I knew everything there was to know about ocular muscles; the diagnosis and treatment, particularly surgical, presented no difficulties. So I thought. Those sublimely ignorant days of cocksure knowledge and confidence were happy ones. I shudder to think of the mistakes I made in the years that followed and shrink from the essential ruthless self-examination of my faults committed since then and even unto the present. "Is there no hope?" sounds a small voice, which I recognize as my own, smothered under conflicting reports of the recognition and cure of ocular muscle imbalance in ten easy lessons. "Yes!" shouts the answer in the united voices of Duane, Lancaster, Bielschowsky, White, Berens, Verhoeff, Peter, and now Prangen.

There is not here a conscientious ophthalmologist, humbled by successes he cannot explain, and humiliated by failures which according to all known rules should have been otherwise, who has not asked himself this question, "Is there no hope?"

Now what can be done about it? It seemed to honest and modest Doctor Prangen that a sort of "back to the farm" movement is about due respecting ocular muscles. For this reason there runs throughout his more or less philosophical paper words and phrases as familiar to the audience as passages from

the Gospel would be to a congregation. This return to old time religion is heart warming. It's danger, however, lies in its familiarity. Fundamental sayings such as "recognition of the abnormal," "unnecessary interference," "careful scrutiny of the troublesome case," "gathering of comprehensive data," "weighing of values," and so on, are evenly distributed so familiarly and so evenly that the back row scoffer impatiently exclaims, "We know, we know," and relapses into his graduate cocksureness.

This paper is one to be read and re-read until each sentence, packed with meat, has been thoroughly digested. It contains many old truths which shine with repetition. It also contains new thoughts such as "the longer an anomaly of either convergence or divergence remains uncorrected, the more certain is the opposing function to become secondarily involved." It long has been known that this is true of the tropias, especially the paretic cases, but that this is so of the phorias demands thought and study for verification. It is my impression that exophoria increases and esophoria decreases with time. Another new thought is the greater value of the measurement of the near point of convergence over the PCb shibboleth. The former can be an accurate clinical value based on experience, the latter an inaccurate scientifically obtained value. Again, in discussing the study of vergence, a new thought expressed is that the ratio of the prism convergence power to the prism divergence power is more important than the actual numerical readings obtained. How often have I been quilty, in measuring these powers, to think of them as separate items, with emphasis of the weaker power.

At the end of the paper are to be found eight points of data to be gathered and evaluated in order to arrive at a diagnosis of abnormal muscle imbalance. One can no more discuss these than he can the ten commandments and for the same reason. They are the sine qua non of proper behavior.

I can do no better than to close with a quotation from the author's paper, with which I am in entire accord. It sums up the entire philosophy of the diagnosis of the phorias. "Muscle diagnosis consists in the weighing of one set of data against the other, trying to figure out the existing relationships and their composite significance. Relationships and relative values count more in diagnosis, I feel, than the actual numerical values found."

THE TREATMENT OF TRACHOMA WITH NEOPRONTOSIL

J. W. Cheney, M.D.
WICHITA, KANSAS

With the advent of sulfanilamide and its derivatives the treatment of trachoma has undergone a complete revolution in the past two years. This paper is written to bring to your attention the efficacy of neoprontosil taken internally and more especially local instillations of the drug in 5 per cent solution in the treatment of trachoma.

In the Middle West there are relatively few cases of trachoma, and most of these occur during the mid-summer following the harvesting of grain. The majority of the cases I have seen are in grade 3, according to the classification by Dr. Max Hirschfelder of the Southern Illinois Trachoma Clinic. These are cases of acute exacerbations of old trachoma in which scarred lids, scarred corneae, marked pannus with photophobia, blepharospasm, and lacrimation are present. I have scanned the literature and have seen no reference to neoprontosil in a 5 per cent solution used locally in such conditions.

In my experience the ideal treatment for trachoma grade 3 is a combination of internal administration of neoprontosil and frequent instillations of the neoprontosil in a 5 per cent solution in the conjunctival cul-de-sac. The success of this treatment depends entirely upon the concentration of neoprontosil in the eye tissues. No doubt a greater concentration is obtained by a combination of the internal and local treatment than by either one alone. However, cases arise in which sulfanilamide or any of its derivatives cannot safely be administered internally, owing either to idiosyncrasies or blood dyscrasias. A blood count and hemoglobin should always be taken before the administration of any sulfanilamide preparation, and the blood should be re-examined at least every seventy-two hours. I wish to call to your attention cases of this type, as they are the ones in which neoprontosil, administered locally, can give splendid results with no discomfort whatever so far as I have observed. I have treated only males between the ages of forty and fifty.

Early in August, 1939, a patient was brought to my office on account of blepharospasm and photophobia. He was unable to get about alone. He gave a history of repeated exacerbations of trachoma requiring long periods of treatment, and examination revealed a grade 3 type. Neoprontosil, grains 10, was prescribed, to be taken orally every four hours, and the next morning he was able to come to my office unassisted. This treatment was continued, and on the sixth day the patient was completely relieved of all the acute symptoms. He stated that his eyes were in better condition than they had been in years.

Another case was that of a man whom I had treated on four different occasions for acute exacerbations, using the old method of treatment, namely, nitrate of silver and copper sulphate applied to the conjunctiva. Each of his exacerbations had required from four to seven weeks of treatment to bring about relief. On this occasion 10 grains of neoprontosil were prescribed, to be taken internally every four hours, and at the end of seventy-two hours it was necessary to discontinue the treatment because of a sud-

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

den marked drop in the red blood cells and hemoglobin. Instillations of a 5 per cent solution of neoprontosil every four hours were commenced, and his condition improved. When the patient was discharged on the fourteenth day, he was in better condition than he had been at any former time following treatment for trachoma.

In the next case treatment was begun in the same manner as it had been in the former cases; ten grains of neoprontosil were prescribed to be taken internally every four hours. However, it was necessary to discontinue administering the drug after forty-eight hours because of a severe gastro-intestinal disturbance. As in the latter case, a 5 per cent solution of neoprontosil was instilled every four hours, and the improvement was continuous. The patient was discharged on the thirteenth day.

I was very favorably impressed by the results obtained from the local instillations of neoprontosil in these cases and could not be convinced that these patients would have ultimately recovered following the short periods of treatment consisting of internal medication only.

In the next case, one of typical grade 3 trachoma, I decided to try the instillations alone. A 5 per cent solution of neoprontosil was ordered to be instilled every two hours. Improvement was rapid from the beginning, and the patient was discharged on the twelfth day.

Another patient was treated in exactly the same manner as the one preceding, and he continued to improve until the ninth day when he developed mild iritis. Instillations of a 1 per cent solution of atropine together with hot applications for twenty minutes every four hours relieved the iritis promptly, and the patient was discharged on the thirteenth day. Pleased with the results of the treatment, he asked for a supply of the 5 per cent solution of neoprontosil to be used at home should he have a recurrence.

In May of this year a patient whom I had treated for trachoma on numerous occasions consulted me, and examination revealed a case of grade 2 trachoma involving the left eye only. The vision in this eye was reduced to 10/200. Instillations of a 5 per cent solution of neoprontosil were administered every two hours, and after eight days all acute symptoms had subsided. His vision had improved to 20/200, which was his maximum vision under normal conditions due to the marked scarring of the cornea.

Early in my experimental work with neoprontosil I asked my confreres, Dr. W. G. Gillett and Dr. G. F. Gsell, to use neoprontosil locally in the treatment of grade 3 trachoma. Doctor Gillett reported fifteen cases in all. Only four of these were the grade 3 type in which I recommended the local instillations of a 5 per cent solution of neoprontosil. The drug was administered three times a day. Splendid results were obtained in three of the cases, but the fourth case did not respond. The other cases of his group were grade 4 trachoma, and little benefit was noted following the treatment. However, I am of the opinion that had he administered the instillations every two hours, the results would have been one hundred per cent in the remaining grade 3 case. I also believe that the others would have shown improvement at least comparable to the results obtained by the old method of treatment with silver nitrate and copper sulphate.

Doctor Gsell reported two grade 3 cases in which the patients were treated with the 5 per cent solution of neoprontosil following which the results were satisfactory.

CONCLUSIONS

I realize that it is difficult to draw a definite conclusion based on the limited

number of cases which I have reported. However, from my own experience and the results obtained by Doctors Gillett and Gsell, I am convinced that local instillations of a 5 per cent solution of neoprontosil should be considered in the treatment of every case of trachoma. It, alone, will effect a cure in the majority of grade 3 cases, and in my opinion this method of treatment is a most valuable adjunct to the internal administration of any sulfanilamide preparation in cases of trachoma.

DISCUSSION

CARL E. RICE, M.D., Washington, D. C.: Doctor Cheney reviews his experience and the experiences of two of his colleagues in treating twenty-three cases of trachoma with neoprontosil. Except for two cases, the neoprontosil was used by instilling a 5 per cent solution into the conjunctival sac at frequent intervals. Under this treatment, Doctor Cheney states that most of the cases were benefited or went on to recovery.

Doctor Cheney divides these twenty-three cases as follows:

GRADE II — one patient.

GRADE III — eleven patients.

GRADE IV — eleven patients.

He indicates that this grouping is based on that used by Doctor Hirschfelder of Illinois. If this classification is similar to that developed by MacCallan, then about 50 per cent of his cases are of the cicatricial type, which probably need only a mild, astringent, cleansing solution most of the time, except for the occasional flare-up of what appears to be trachoma.

There is no doubt in my mind but that the use of sulfanilamide and its derivatives constitute a real step forward in the treatment of this disease. Apparently in those diseases where sulfanilamide has found its greatest usefulness, its effect has been accomplished by the sulfanilamide portion of the molecule. One can but wonder whether the neoprontosil, instilled into the conjunctival sac, remains there long enough for the neoprontosil molecule to be broken down and the sulfanilamide liberated, or whether the lysozyme of the tears is even able to effect such a change under any conditions. It is possible that the neoprontosil instilled in the conjunctival sac accomplishes its results merely by the mechanical cleansing effect.

One must remember that trachoma in not a few cases is a self-limited disease, and it may go on to arrest or possible cure without any treatment. Also, trachoma can be overtreated, especially in the later stages. I have seen some cases of trachoma, especially in the later stages such as Doctor Cheney has presented in this series, improve and become arrested under irrigations of nothing more than boric acid solution.

I would respectfully suggest that in Doctor Cheney's next series he treat only one eye in any case with neoprontosil and that the other eye be treated with some bland solution, such as normal saline, boric acid, and so forth. Approached in that manner, treatment with neoprontosil can more nearly be judged for its special value in trachoma when the drug is instilled in the conjunctival sac.

It seems to me that one of the great values of sulfanilamide in the treatment of trachoma is the possibility of getting at this eye disease through the general practitioner who, up to now, could be of little help to the patient.

It is highly desirable for ophthalmologists to pursue all possibilities in developing the use of sulfanilamide in cases of trachoma, as Doctor Cheney is doing. In that way, a new therapeutic agent may be placed in the hands of the general practitioner that will help to eradicate this disease before too long.

HARRY S. GRADLE, M.D., Chicago: Doctor Cheney's observations with regard to the use of a 5 per cent solution of neoprontosil in the local treatment of trachoma are most interesting, and they open a field for further investigation in the modern breath-taking treatment of this century-old disease. My own experience has been concerned primarily with the internal administration of sulfanilamide; consequently, I am not in a position to either corroborate or to deny Doctor Cheney's results.

In response to my question, Dr. Polk Richards, the distinguished trachomatologist of our Indian Medical Service, wrote to me as follows:

> As far as I know, none of our physicians have used solutions of neoprontosil by instillation in treating trachoma. We plan, when the schools convene this fall, to test the local administration of both neoprontosil and sulfanilamide on groups of untreated children. We shall use it over an extended period of time and shall note results, if any, from time to time.

Incidentally, when Doctor Richards talks about groups of untreated children in the

Indian Service, he refers to groupings of hundreds at a time.

A doubting Thomas is Sie-Boen-Lian who reported the following in the December, 1931, issue of Ophthalmologica:

> Local applications of sulfanilamide should free the patient of any possibilities of unpleasant by effects. For this reason, I treated a great many patients with local instillations of prontosil in 2½ to 5 per cent solutions. In one case I even injected a 5 per cent solution under the thickened conjunctiva. In this latter case not only was there no improvement in the tracoma but the pannus even advanced during the treatment. The cases of trachoma that were treated locally with a solution of prontosil did show a definite decrease in secretion, but the pannus remained unchanged. Good results only followed the oral administratoin of the drug.

The greatest die-hard of all, however, is the old Egyptian Master, A. F. MacCallan, who, now that he is located in London, no longer sees very many cases of trachoma. Consequently, his condemnation of sulfanilamide and its congeners, as expressed in the October, 1939, issue of the Revue Internationale du Trachome, must be evaluated as a purely theoretical expression.

So, let us be fair in our condemnation or approbation of any new method of treatment, such as Doctor Cheney proposes. Let us base our views upon personal observations and not theoretical considerations. Above all, let us remember that the report of any therapeutic results obtained in trachoma must include:

1. The extent of previous treatment.
2. The stage of the disease when the new treatment was started.
3. The presence or absence of secondary infection.
4. The condition of the cornea.
5. The length of observation of the case after treatment was instituted.

LAWRENCE T. POST, M.D., St. Louis: During the past summer, Doctor L. A. Julianelle of Washington University, Doctor J. E. Smith from Loyola, and Doctor G. H. Gammett, who was assisting Doctor Smith at the time, treated twelve cases of previously untreated trachoma most of which were third stage. Nine of them were treated at the Washington University Clinic, and three of them at Loyola. Neoprontosil in a 2½ per cent solution was used, not the 5 per cent solution that Doctor Cheney used. Instillations were made not as frequently, but four times a day. The treatment was continued for four weeks. The patients were instructed with regard to instilling the drug and carrying out treatment at home. In every case there was marked improvement for approximately a week. At the end of that time and for the remaining three weeks there seemed to be no further improvement, and it was necessary to resort to other drugs.

J. W. CHENEY, M.D., Wichita: I wish to thank the doctors for their comments.

There is one thing about the cases that I have treated so far, namely, they were treated in an institution where, if there had been any recurrences, they certainly would have been noted. Up to date, in the cases that I have treated and have reported, there has not been a single recurrence in over a year.

I still firmly believe that the best method of treatment is the internal treatment combined with the local treatment. I believe it will give one hundred per cent results if used.

THE TREATMENT OF RETINOBLASTOMA (RETINAL GLIOMA) BY A COMBINATION OF SURGERY AND RADIATION

HAYES E. MARTIN, M.D.*
BY INVITATION
and
ALGERNON B. REESE, M.D.†
NEW YORK

IN 1936 we published a preliminary report[1] on the treatment of bilateral retinoblastoma by a technic of fractionated radiation which had not previously been used for this form of cancer. That report was based upon six cases of bilateral growths in which one eye had been removed and the other irradiated in an attempt to control the growth and conserve vision. One of the purposes of this communication is to give additional information to date in these six cases and to submit preliminary data on four more recent cases of bilateral retinoblastoma in which the treatment was similar.

In the present report we shall also discuss the other clinical forms and stages of retinoblastoma, namely, unilateral tumors, advanced bilateral growths with the vision irreparably destroyed on admission, and postoperative recurrent and widely disseminated retinoblastoma, in which radiation therapy as a means of conserving vision is not applicable.

SELECTION OF TREATMENT FOR RETINOBLASTOMA

An ideal method of treatment for retinoblastoma would eradicate the growth and leave normal vision in both eyes. Unfortunately, such an ideal so far has been impossible of attainment. In the first place, a malignant tumor of the retina, even though small, cannot be removed surgically without enucleation of the eye. Secondly, whether the growth be unilateral or bilateral, the disease is invariably so far advanced as to have irreparably destroyed vision in at least one eye before there are sufficient objective or subjective symptoms to permit making a diagnosis.

If the growth be unilateral, there can be no question but that the safest plan is to enucleate one eye immediately, being content with the remaining monocular vision. If the disease be bilateral, the best result that could be hoped for would be brought about by enucleating the eye in which the growth is farther advanced and conserving vision, if possible, in the other eye with radiation therapy.

When the involvement of both eyes is so extensive that no vision in either can be conserved by any means, radiation has no practical advantage over enucleation of both eyes, since in either case total blindness is inevitable. As a matter of fact, radiation treatment is contraindicated in these advanced cases since even a moderate delay in the complete eradication of the growth unquestionably increases the danger of wide dissemination. The cosmetic appearance following enucleation of the eye is supe-

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

* Attending Surgeon, Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, N. Y.

† Ophthalmologist, Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, N. Y. Attending Surgeon, Institute of Ophthalmology, New York, N. Y.

rior to that which follows complete sterilization of an advanced orbital growth by radiation. In brief, the only indications for radiation in retinoblastoma are: (1) to treat early growths in an attempt to conserve vision in one eye and (2) to treat residual or postoperative recurrences of the tumor.

The selection of the method of treatment in a given case of bilateral retinoblastoma is somewhat empiric and may depend largely upon past experience in therapy and the success or failure in similar cases. If the bilateral growths are believed to be too far advanced to permit any reasonable chance of conserving vision in either eye by radiation, it is our opinion that bilateral enucleation should be done immediately. In our previous report we held what would probably even now be the general medical and lay opinion on this subject, namely, that the removal of both eyes, thereby immediately blinding a child, would not be justified even though it saved life. Since that time, however, after observing the terminal courses in two cases, we have altered this opinion. One of the patients (case 22, figure 1) was considered incurable on admission, and the policy of treatment originally decided upon was that of "noli me tangere." As the disease progressed, however, the primary tumors produced painful, bulky enlargements of the globes which protruded between the lids, with corneal ulceration, perforation of the eyes, and sepsis, with so much local

FIG. 1 — TERMINAL STAGES OF UNTREATED BILATERAL RETINOBLASTOMA (Case No. 22). Both globes are buphthalmic and proptosed; the latter is so marked on the right side that there is corneal ulceration and some necrosis of the exposed tissue. The left cornea is steamy but tumor tissue can be seen in the anterior chamber. A few days after this picture was taken it was necessary to enucleate the right eye for hygienic reasons and to relieve the patient of constant pain. A month later, the left eye was enucleated for the same reasons. This case illustrates the indication for bilateral enucleation for hopeless cases of bilateral retinoblastoma as soon as permission can be obtained in order to prevent unnecessary suffering which will eventually compel enucleation of the eyes with no hope of saving life, since by that time the disease has become widely disseminated.

pain that several months before the patient's death we were compelled to remove first one and then the other eye for palliation. Leaving the eyes in place, until their removal was obligatory, accomplished no useful purpose and only permitted the certain wide dissemination of the growth when life possibly might have been saved by immediate bilateral enucleation. The second patient, whom we saw in consultation only on three occasions, had been treated elsewhere. Enucleation of one eye had been performed, and irradiation to the other had been administered. Irradiation failed to control the growth of the tumor, and the last time we saw the child, the growth obviously was extending, and there was only a slight amount of vision remaining. At that time we advised enucleation of the remaining eye in an attempt to save the patient's life, since the child soon would be blind in any case. The eye already had begun to be painful, but there was as yet no evidence that the disease had extended beyond the globe. The parents would not consent to the operation, and the child died about three months later, possibly solely from local effects of the tumor.

Even though blindness results, it is surely more humane to strive for a complete cure of the disease and survival, thereby effecting a normal span of life, than to select for the child the doubtful privilege of rapidly diminishing vision for a few weeks followed by inevitable complete blindness and a painful death after several months of suffering. We have had to settle such a question recently in the case of a child with bilateral retinoblastomas in which there was only slight vision in one eye. After a frank discussion with the parents, reviewing with them the clinical histories in similar cases, the unanimous verdict was that both eyes should be removed immediately. Following bilateral enucleation there has been no recurrence of the growths up to the present time and the child, otherwise healthy, is attending a school for the blind (case 23).

Is it not presumptuous for anyone — parent, physician, or lay-committee — to decide arbitrarily for a child that death is preferable to life without eyesight? It is a curious fact that, in those cases which have attracted so much attention in the public press, the suggestion never has been made to have this question referred to a committee of adults who themselves had been blind since childhood. Such a committee probably would not agree unanimously that death is preferable to blindness. Since the wishes of the one most concerned — the child — cannot be consulted, it seems only fair that life should be spared him at least until he is old enough to decide for himself. If death is considered preferable to blindness in cases of advanced retinoblastoma, then the non-interventionists logically should assume also the responsibility for disposing of these patients by euthanasia when the disease reaches the painful terminal stages in order to prevent the weeks or even months of intense suffering. It is our opinion that anyone who has followed even a single case of this form of cancer through its terminal stages will consider it inhumane to withhold immediate enucleation of the eyes which, if not effecting a cure, at least will have a chance to obviate much suffering. Sentimentalism in medicine, although well-intended, too often completely disregards the interests and welfare of the patient.

In postoperative recurrent retinoblastoma the prognosis is by no means hopeless, for the tumor still may be limited to the apex of the orbit and therefore is amenable to permanent control by radiation. When the growth is widely disseminated, palliative radiation or surgical excision of painful foci of

the growth is definitely worthwhile from the humane standpoint.

On the basis of the foregoing general principles of treatment, cases of retinoblastoma may be classified into four groups, as follows:

CLASSIFICATION OF RETINOBLASTOMA FOR SELECTION OF TREATMENT

	TREATMENT METHOD
1. Unilateral tumor not extending outside of globe.	Enucleation of the globe.
2. Bilateral tumors.	(a) Enucleation of the more advanced eye and treatment of the other by fractionated radiation if there is a chance of conserving vision. (b) Enucleation of both eyes if the vision is irreparably destroyed.
3. Residual* or recurrent tumors following enucleation.	Radiation.
4. Widely disseminated retinoblastoma.	Palliative treatment by radiation or surgical excision of individual painful lesions.

* Tumor left in nerve or orbit at time of enucleation.

The rationale of treatment will be discussed first under these headings, followed by a detailed description of technic under separate headings.

Unilateral retinoblastoma not extending outside the globe. — As we have previously mentioned, retinoblastoma is invariably far advanced when first diagnosed, and our attempts to treat unilateral tumors by irradiation never have been successful in eradicating the disease and conserving any vision in the treated eye. In those few instances (cases 1 and 2, figure 2), in which we have made the attempt, the improvement of these bulky unilateral tumors under several weeks of radiation was not particularly impressive, and we found little to encourage us in the belief that a conservative result (retention of vision with cure of the tumor) could be obtained. If vision could not be conserved by radiation, we were forced to admit that while we were thus temporizing, we undoubtedly were giving the cancerous growth the opportunity to disseminate widely and for this reason we discontinued the irradiation and enucleated the eye. Since 1936 we have not used radiation in unilateral tumors, and at the present time we urge the immediate enucleation of the affected eye.

Bilateral retinoblastoma. — We have already discussed our reasons for advising immediate bilateral enucleation when the growths are so far advanced that there is no hope of conserving vision in either eye by radiation.

When there is a chance of controlling the disease in the less involved eye with conservation of some vision, we advise the immediate enucleation of the eye in which the disease is more advanced and radiation therapy to the other. Such radiation therapy is complicated and time consuming and is possible only by the use of special apparatus and by careful attention to many technical details. It is probable that such treatment should be given only in specialized clinics where there is sufficient material for the accumulation of adequate experience both in administering the treatment and in observing the subsequent course by systemic ophthalmoscopic examinations. When there is sufficient clinical material and the average facilities for radiation therapy, it should be possible to develop a satisfactory technic, and we hope that

FIG. 2 — UNILATERAL RETINOBLASTOMA (Case No. 2). *(a)* The tumor mass gave a white reflex through the dilated pupil of the right eye on admission five months after the mother had first noticed the abnormality of the eye. *(b)* Complete disappearance of the white reflex after irradiation. With the ophthalmoscope, though, it seemed that the lesion in the retina was arrested, but there was a large globular elevation which was thought to represent tumor-growth in the choroid. This patient died of generalized metastases.

FIG. 2 *(c)* — The tumor is seen growing as a large mass in the uvea; it is divided by a connective tissue septum at about the junction of the ciliary body and choroid. The overlying retina is somewhat detached and is apparently free of viable tumor tissue.

the report of our experiences and the description of our technic and apparatus will serve a useful purpose.

As we have previously mentioned,[1] retinoblastoma is a radioresistant neoplasm which cannot be controlled by moderate radiation dosage except in rare instances.* Although the eye itself is fairly tolerant to radiation, every possible precaution must be taken to protect the lens and conjunctiva from the direct beam if the growth is to be destroyed and a useful amount of vision conserved. By using special protective measures, fractionated radiation is directed to the posterior portion of the orbit and the growth over a period of from four to five months at as high a rate as possible without producing effects so acute that the treatment must be discontinued. If successful results are to be obtained in these cases, the physician and the parents should realize in the beginning that the course of treatment will be tedious, time-consuming, and onerous, that each daily set-up and each minute the child remains under the x-ray machine require the most scrupulous attention to the minute details of the technic, and that failure certainly will result from repeated neglect of these details. We know of instances in which, following our original publication, attempts have been made to treat retinoblastoma by the fractionate radiation principle without proper attention to the important details; namely, the child's head was not held in position during treatment, the skin portals were so large as to include the entire globe, and the total doses were small. So far as we know, all of these attempts were unsuccessful, and we are convinced that unless proper attention is given to details, irradiation of retinoblastoma is hardly worthwhile since any casual attempt is doomed to failure from the beginning.

Residual or recurrent retinoblastoma after enucleation. — Even though there be an inoperable recurrence in the orbit after enucleation, the prognosis is not hopeless provided that one realizes that retinoblastoma is a radioresistant tumor requiring heavy x-ray dosage which, to be tolerated, must be confined to the relatively small volume occupied by the tumor. Lethal doses for cancer over a large volume of a child's head will be serious and even may be fatal. The refinements in radiation technic, however, need not be so rigid as when the globe is present and the function of vision is to be conserved. The methods of radiation used for such recurrences are about the same as for other superficial growths, and the technic will be described in a separate section.

Following enucleation, the optic nerve should be severed flush with the sclera and prepared immediately as biopsy tissue to determine whether or not the operative section was beyond any possible tumor invasion of the nerve. If the examination indicates that tumor tissue is present in that portion of the nerve remaining in the orbit, then we believe that immediate and adequate radiation is indicated rather than an exenteration. As we shall record in the section on "End Results," the chances of cures in our cases of residual tumor in the optic nerve stump were about four times as good when the radiation had been started immediately after operation instead of deferred until the recurrence was visible and palpable in the orbit.

* In our previous report,[1] we reviewed the literature on the radiation treatment of retinoblastoma and discussed in detail the three reported radiation cures, calling attention to the fact that, in general, the doses were small, about 1/50th of that which we have found necessary. The number of reported spontaneous cures of retionoblastoma far exceeds the number of previously recorded radiation cures, and it is entirely possible that the alleged radiation cures by these small doses were the result of coincidence with a spontaneously regressing tumor. In any event, we are convinced that the attempt to control retinoblastoma by these minute doses of radiation is illogical and unjustifiable.

Widely disseminated retinoblastoma. — The care of a child with widely disseminated cancer of any variety is a hospital problem, since these young patients require constant nursing care and other facilities which are not available in the home. Too often the patient with incurable cancer receives inadequate attention for the relief of the various complications which arise during the terminal stages of the disease. The common tendency toward the administration of opiates alone is not a solution of this problem. The suffering of the child with widely disseminated retinoblastoma can be alleviated markedly by intelligent nursing care and aggressive treatment consisting of surgery or radiation to the more painful foci of the disease.

TECHNIC OF FRACTIONATED RADIATION TREATMENT FOR RETINOBLASTOMA

The general principles for the treatment of retinoblastoma by fractionated irradiation which we now employ are similar to those described in our previous publication,[1] but as the result of further experience, we have made several important modifications in the technic of treatment and in the apparatus. The general principles are: (1) two small skin portals (2.5 cm. in diameter), (2) accurate direction of the beam of the roentgen rays, (3) multiple treatments (50 to 60), and high total dosages expressed in roentgens (9,000 to 10,000 r or even more per portal). The modifications in technic which we have introduced since our former report are: (1) an improved design of the apparatus used which favors more accurate direction of the beam and protection of the cornea, lens, and conjunctiva, (2) the elimination of a direct beam through the pupil of the eye, and (3) standardization and systematization of the interval and size of the individual and total doses.

Physical factors of roentgen radiation. — In order that the greatest possible proportion of the skin dosage reach the tumor, it is essential to employ high voltage roentgen rays (200 to 250 K.V.) with a filter of 0.5 — 1.5 mm. copper and long target skin distances (60 cm. or over). High intensities (milliamperes of current) are indicated so as to cut the time of the treatment down to the minimum. Except for the size of the skin portals, obtained by special cylinders as will be discussed in a succeeding section, these physical factors of the radiation are within the scope of most clinics. The exact physical set-up which we now use is as follows: 250 K.V., 30 milliampere current, filter 1.5 mm. copper, target skin distance 60 cm., circular portals 2.5 cm. in diameter, intensity of about 50 roentgens per minute. The usual single dose of 400 r therefore can be given in about eight minutes.

Size, shape, number and location of skin portals. — In the intensity necessary for the control of retinoblastoma, all radiation which strikes the uninvolved portions of the eye or surrounding structures is not only useless but distinctly harmful. Therefore, if one is to deliver an adequate dose to the growth safely, it is essential that the beam of roentgen radiation be confined as much as possible to the immediate area of the tumor. Since the beginning of this work in 1933, we have used small circular portals, 2.5 cm. in diameter, which we still believe to be the optimum size. Larger portals cannot be used if the highly injurious effects of direct irradiation to the cornea, lens, and conjunctiva are to be avoided.

Since our preliminary report, we have devised two special cylinders for this purpose, detailed descriptions of which are given in figures 3 and 4 and their accompanying legends. By the use of these devices, radiation may be confined to a beam of small caliber which is aimed at the posterior wall of the globe, much

as one sights along the barrel of a rifle at a small target, avoiding irradiation of the cornea and lens by the direct beam. With further experience we have concluded that the posterior wall of the globe can be irradiated safely only from two cutaneous portals in the positions illustrated in figure 4, rather than from the three portals which we formerly advised. These two portals are designated as (1) the temporal portal which is lateral to the outer canthus and (2) the nasal portal on the opposite side of the bridge of the nose, the beam being pointed contralaterally and slightly backward.

We originally used a third portal with the beam pointing directly backward through the pupil of the eye. We now are convinced that this anterior portal should not be employed because we never were able to administer any great quantity of radiation through this portal (about 2500 r) without bringing on troublesome complications — chiefly radiation conjunctivitis and corneal changes. The latter constitute the main deterrents to the administration of a lethal dose of radiation for cancer to the posterior wall of the orbit. The omission of this anterior portal always reduces the degree of these undesirable radiation effects in the anterior portion of the globe, which nevertheless may occur from the other two portals if the beams are not accurately centered and directed.

Maintaining the globe in its correct relation to the fixed and limited beam of roentgen radiation during treatment. — This is extremely important and is a rather difficult task which requires both patience and tact. Even small errors in the direction of the narrow beam are of

FIG. 3 — SPECIAL CYLINDERS FOR RADIATION TREATMENT OF RETINOBLASTOMA. *(a)* Has an oblique distal end to fit against the temple. *(b)* Is applied to the bridge of the nose to irradiate a growth in the retina on the contralateral side. It has a hooked projection to mark the margin of the beam of radiation so that the cornea and anterior chamber of the eye may be spared. (These devices were constructed in the Machine Shop of the Memorial Hospital for the Treatment of Cancer and Allied Diseases by Mr. A. Schreiner, Master Mechanic.)

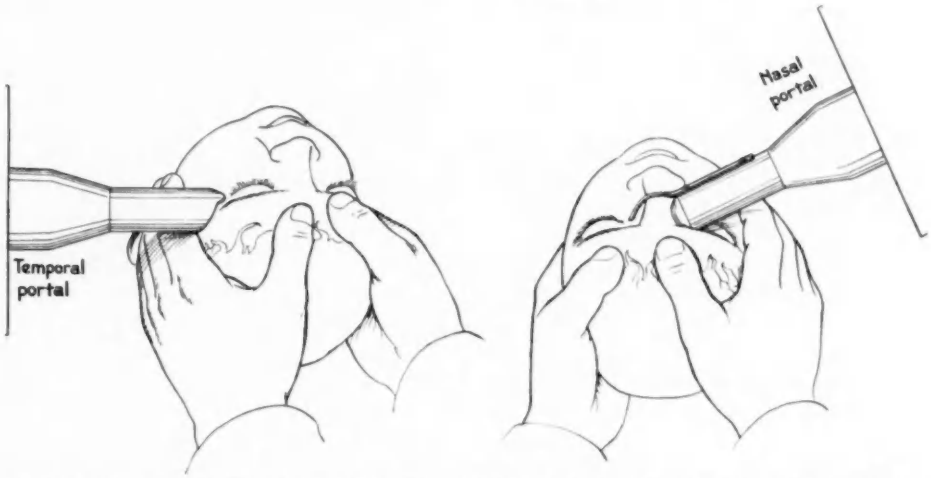


FIG. 4 — **ROENTGEN IRRADIATION OF RETINOBLASTOMA.** *(a)* The child's head is being held in position for irradiation of the posterior half of the left globe through a temporal portal. *(b)* The child's head is being held in position for irradiation of the posterior wall of the left globe through the opposite side of the bridge of the nose.

FIG. 4 *(c)* The child's body is immobilized by wrapping it in a sheet. One of the parents steadies the child's body and the other holds the head in position during the treatment.

sufficient significance to determine the difference between success and failure. By the use of special devices, described in figures 3 and 4, the beam of radiation is aimed at the posterior wall of the globe, care being taken that it does not strike the anterior wall (cornea and lens). After being placed in position, the child's head is held in direct and steady contact with the cylinder during treatment.

Up to the age of 5 to 6 years, a child cannot be expected to cooperate, and someone must hold the head firmly in the proper postiion. This task, we believe, is the duty of the parents or other members of the family rather than of any member of the medical, nursing, or technical staff. The holding of a crying, struggling baby in a fixed position for ten minutes three times a week over a period of three to four months is onerous, and the slight risk of general body exposure from remaining so close to the x-ray tube and the possibility of local exposure to the hands while holding the head is one which should be assumed by the family of the child, who have to go through the experience in only one case, rather than by members of the staff who might also have to undergo it in other cases. Ordinarily one parent holds the child's head and the other the body, which is partly stabilized inside a folded bed sheet. These positions and the location of the portals are illustrated diagramatically in figure 4.

At the beginning of treatment the parents naturally may be in a highly emotional state, and even though they have the best of intentions and try to understand the importance of their duties, nevertheless they may find it difficult to carry out instructions. By patiently and repeatedly explaining the importance of this duty and the reasons for the parents' undertaking it, and by giving simple descriptions of the local anatomy with regard to the tumor (figure 5) we have found that the average parents will do their part quite acceptably after the first two to three trials.

Size of the individual doses, frequency of treatments, total period of treatment and total dose. These factors must be considered together since each one depends so much upon all the others. With the physical factors already described, we have found that the individual dose should be about 400 r if giv-

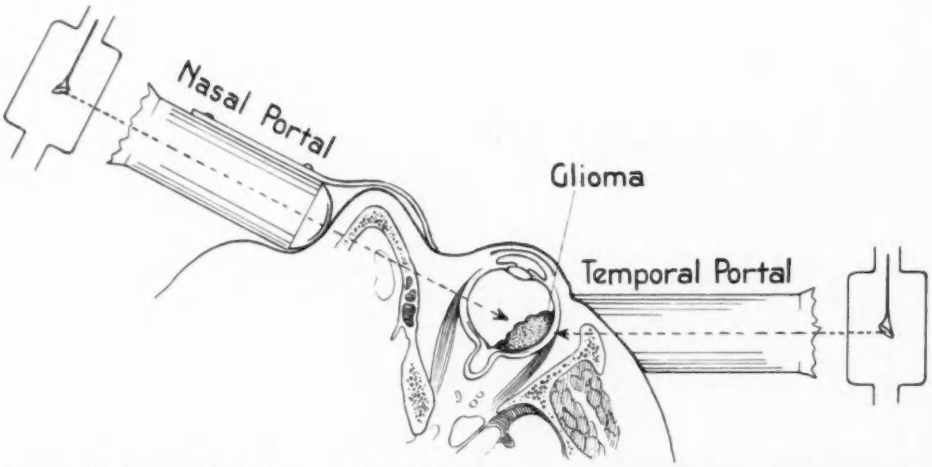


FIG. 5 — LOCAL ANATOMY OF THE TUMOR — Cross section diagram showing the path and the objective of the roentgen radiation as directed through each of two portals.

en three times a week. In deciding the frequency of treatments, one must compromise to some extent between what would probably be the ideal treatment—that is, daily exposure requiring daily trips to the clinic by both parents and child, which might be impractical or even impossible for both financial and physical reasons, and the alternative plan of giving larger doses at longer intervals. When the home is at some distance from the clinic, it usually is necessary to admit the child to the babies' ward for a period of several months while treatment is being given. In other instances, the child, living nearer, may remain at home. In either case we have found that on the average, both the parents and the child can make three visits a week to the clinic, if necessary, over a period of several months.

When treatment is given three times a week, the two portals (temporal and nasal) are exposed alternately so that each area is irradiated about every fourth day. Under such a plan the treatments are given regularly without interruption, aiming at the eventual administration of about 8,000 to 10,000 r through each portal, which will require about 16 to 18 weeks. After the administration of about 2400 r through a portal, an erythema develops in the skin exposed to the direct beam which, during the next four to five weeks, may go on to a mild epidermicidal reaction. Such an effect should be welcomed since it indicates that radiation is being delivered at the optimum rate. After this reaction has developed in the skin it usually proceeds to heal partially while the treatment is being continued at the same rate as that which produced it, a phenomenon frequently observed in radiation therapy of cancer in general.

Dosage control by observation, externally, and ophthalmoscopically. As previously mentioned, the appearance of radiation erythema developing into a mild epidermicidal reaction of the skin of the temporal and nasal portals need not be the cause for alarm. On the other hand, the development of marked conjunctivitis and keratitis with photophobia indicates that there has been an error in the direction of the beam either in the original set-up or by failure to hold the head steady in its correct relation to the cylinder. If these reactions are not too severe, the treatment may be continued with more careful precautions to avoid including the anterior portion of the globe and the conjunctiva in the direct beam. If the misdirection of the beam continues, these effects may become so severe as to necessitate the cessation of treatment. In three of our patients, these severe reactions in the anterior portion of the eye have caused partial failures, namely, the loss of vision even though the growth was permanently controlled (cases 7, 8 and 11).

Ophthalmoscopic examination with careful comparison of the appearance of the lesion with preceding examinations should be carried out at 2 to 4 week intervals, but despite the ophthalmoscopic appearance, the radiation should be continued to a dose of at least 7500 r to each portal before termination of treatment is even considered, since the latter dose is invariably well tolerated if properly administered. Depending on a lesser dose will too often result in incomplete regression. If there is any doubt about the sterilization of the tumor, the treatment should be carried beyond 8000 r per portal and continued to at least 10,000 r if necessary. Beyond this point further treatment is of doubtful value, since the untoward local effects of radiation are considerable.

CLINICAL COURSE UNDER FRACTIONATED RADIATION

During the course of treatment and for one year afterward, each of our pa-

tients has had an examination of the eye every month under general anesthesia. This included an ophthalmoscopic examination through a dilated pupil and determination of the tension with the tenometer. Notes, diagrams, and sketches have been made to compare variations in the appearance of the lesion from time to time. In some cases drawings have been made by an artist before treatment was started and after its completion. After treatment was finished and a year had elapsed, all the cases in this series were followed every three months up to the present time.

Cloudiness of the retina surrounding the lesion. — Within the first month after the beginning of treatment, a grayish to yellow-white zone develops in the retina surrounding the lesion, apparently due to edema adjacent to the tumor. This phenomenon may be observed at any time through the course of treatment. The zone is sometimes outlined by a highly refractile reflex ring running concentric to the border of the lesion. In some instances it seems to represent a flat detachment due to the accumulation of a subretinal transudate, particularly in the dependent portion. Such retinal cloudiness must not be confused with a later complication resulting from the extension of the tumor into the choroid, which will be discussed under complications.

Alteration in the contour of the lesion. A change in contour can be followed either by measurement with a grid projected into the ophthalmoscopic field or, less accurately, by estimation in disc diameters. After one to two months there is usually a recession of the borders of the tumor which often become rarefied, feather-edged, and irregular in contour. This irregularity often appears first in the upper half while the lower half seems more sharply demarcated and even overhanging. We have interpreted these phenomena as indicating sufficient dissolution of the tumor tissue to permit it to gravitate somewhat to the more dependent portion, thereby leaving a receded upper border and a sharper somewhat pendulous lower border. Recession of the border proceeds slowly over a period of from 2 to 6 months, as the broken-down tissue is absorbed. The area over which the tumor recedes around the base is identified by a disturbance of the pigmented epithelium which produces either proliferation and resultant pigment changes or complete disappearance, resulting in a brighter red reflex from the underlying choroid. Such an appearance indicates recession only at the base of the lesion and not of that part of the tumor which protrudes into the vitreous. Nevertheless, the appearance of this change in the pigmented epithelium, which is seen from the first to the fifth month, is evidence of regression and as such its accurate location and extent are important.

Decrease in the height of the lesion. We have attempted from time to time to estimate the height of retinal lesions in diopters, a method which did not prove satisfactory since the margin of possible error was disproportionately large in comparison with the height which we were trying to measure. It is obvious, however, that there is usually a decrease in the height of the lesion commensurate with the recession of its border. As the height decreases, the surface of the tumor usually becomes more irregular in contour.

Vascularity. After from 2 to 6 months the increased vascularity over the surface of the lesion should diminish. This decrease should be progressive, and an increase in the number of vessels in any area is evidence that there is a continuation or resumption of growth. In two cases we noted an increase in the vascularity of the lesion at one site just

after the originally intended course of radiation had been completed, and in both we resumed treatment. In two other instances, six months and one year, respectively, after treatment was started, we noted the appearance of beds of newly-formed capillaries together with several small petechial hemorrhages. We interpreted this as representing collateral circulation which had developed following vascular atresia and since both of the patients have remained free of disease, this finding was not an indication of tumor activity.

Calcification. — It is well-known that calcification frequently occurs in a non-irradiated retinoblastoma. Calcium is usually seen in the microscopic sections, and Pfeiffer,[2] by roentgenograms, has demonstrated its presence in 75 per cent of the casess which he has examined. Viewed with the ophthalmoscope, small irregular, chalky to pearly-white granular areas of calcification can be seen over the surface of the lesion, which, in our opinion, are pathognomonic of a retinoblastoma and are never found in the various forms of pseudoretinoblastoma. In the microscopic sections of a true retinoblastoma, the calcium is seen in the areas where the tumor tissue has outgrown its blood supply and become necrotic. The treatment of these tumors with roentgen rays according to the method described here tends to cause additional necrosis of the tumor tissue and more deposition of calcium, and ultimately the lesions are reduced for the most part to necrotic tissue and calcium (figures 8a, 8b, and 8c). The former tends to absorb gradually while the latter persists. The end-stage then is often a somewhat elevated chalky to pearly-white avascular mass composed mostly of calcium and surrounded by some pigmentary changes (figure 6). The actual and relative increase in the calcium content of the lesion as observed ophthalmoscopically is one of the best indices of regression. The

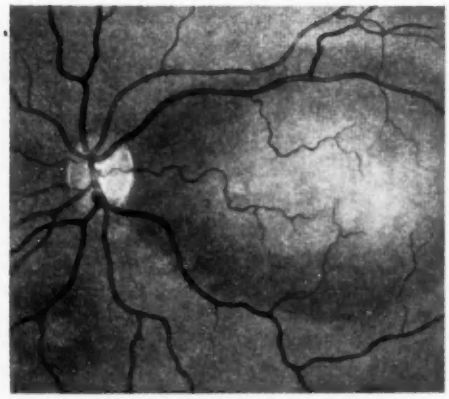


FIG. 6 *(a)* Diagrammatic sketch of a lesion before treatment. The larger lesion extends from the temporal margin of the disc to well beyond the macular region. There is a smaller lesion below the disc.

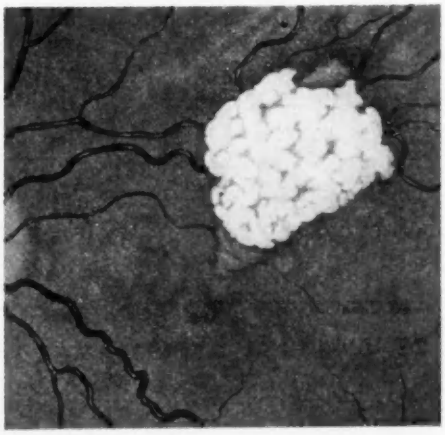


FIG. 6 *(b)* A drawing of the larger lesion at the completion of the treatments. There is an elevated chalky-white mass with undulating surface and irregular borders. At the upper and lower borders there is a pigmentary disturbance.

increase in the calcium element may be noted from the first to the sixth month. In one of our arrested cases with good function (case 13, figure 7) — too recent to be considered a permanent cure — this calcification has appeared only in a small degree.

Hemorrhages. — Small hemorrhages, which eventually absorb, may occur over the surface of the lesion at any

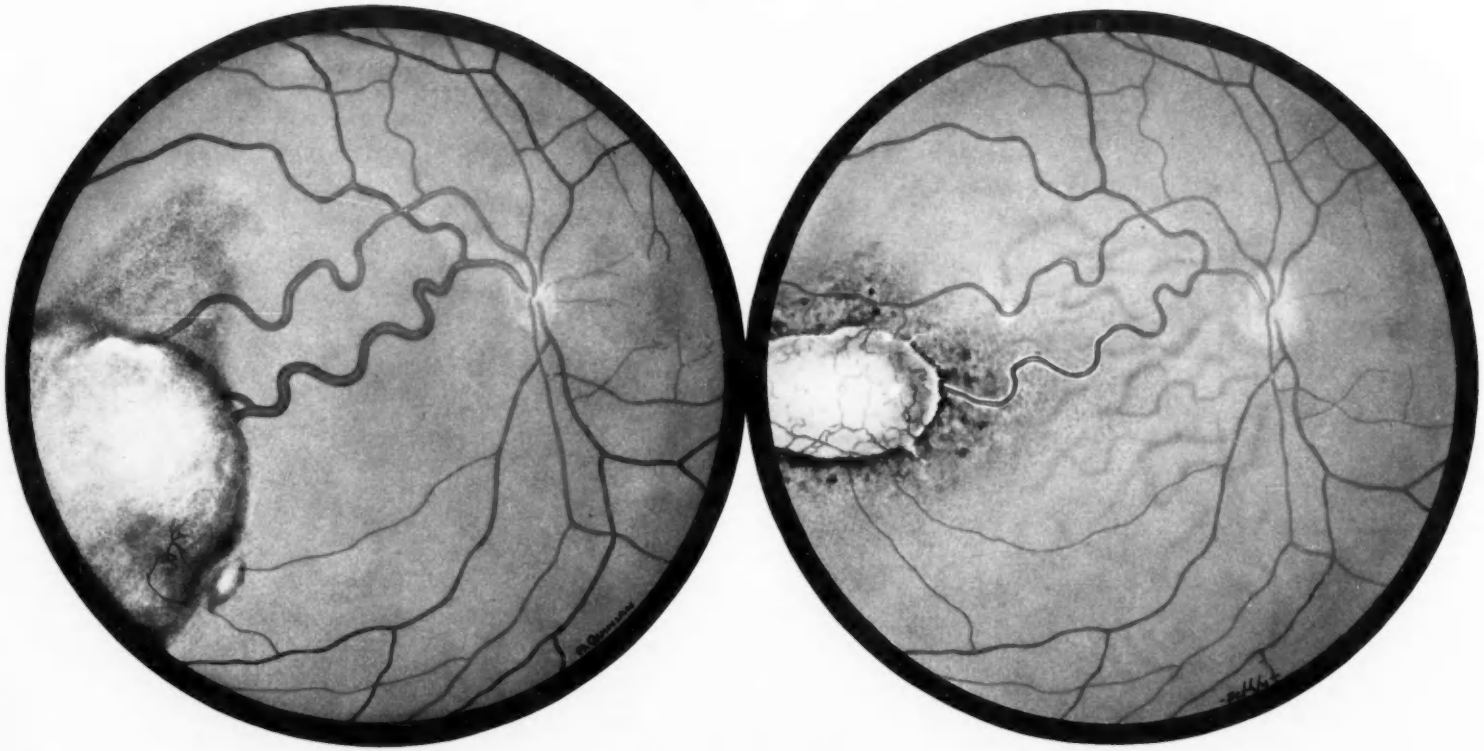


FIG. 7 — CASE No. 13

(a) Left eye. Appearance of tumor before treatment.

(b) Left eye. Appearance of tumor after three months of treatment. Several small white foci of calcium can be noted over the surface.

(OPPOSITE PAGE 82)

UNIV. OF MICH.

time from the first to the tenth month and are sometimes found in proximity to a bed of newly-formed capillaries (see "Vascularity"). In our cases no large hemorrhages of consequence have been observed. In one advanced case (case 8) in which atrophy of the globe developed, a hyphemia was noted.

Atrophy of the iris with dilatation. In two of the arrested cases (cases 8 and 11) atrophy of the iris developed following secondary glaucoma after one year and after sixteen months, respectively. The pupils became quite wide and immobile to light, probably due to an atrophy of the iris.

Posterior synechiae. In one instance, after about fifteen months, some posterior synechiae developed, probably as the result of a mild iritis from dissolution of the tumor tissue by radiation.

Implantation growths on the iris. In two cases, after sixteen and eighteen months, respectively, which were not controlled by radiation, there appeared on the anterior surface of the iris several small foci of vascularized tumor tissue, representing fragments of the growth which had gained access to the anterior chamber and implanted themselves on the iris where they found sufficient blood supply to grow. These were far-advanced cases which were obviously out of control and terminated fatally.

Extra-ocular and adnexal changes. — The reaction of the skin, conjunctiva, and cornea to a given dose of radiation will vary widely in different individuals. Some patients will show only a mild degree of erythema in the skin at any time, while in others this reaction may go on to a superficial blistering. A variation of lesser degree occurs in the conjunctiva and corneal reaction, but severe changes in the reaction in the latter structures are most often due to errors in direction of the beam than to individual hypersensitivity. If an accurately measured dose of 400 r (calculated in air) is given three times a week by the technic which we have described, the absence of a marked erythema in the skin does not necessarily mean that the dose is ineffective, for some of our best results have been obtained in patients who have shown only mild external reactions. On the other hand, the doses above-mentioned should produce a slight blistering of the skin in at least 75 per cent of the patients treated. Otherwise there is probably some error in the physical measurements of the output of the x-ray machine. As has been mentioned, a blistering reaction in the skin need cause no alarm. A bland ointment (vaseline or boric acid ointment) should be applied to the affected area, which usually partially heals during the course of treatment.

During the course of the treatment some of our patients have developed photophobia and a blush of the eye accompanied by slight changes in the corneal epithelium. In these, there was a diminution in the lustre over the lower one-third to one-half of the cornea, and upon staining the cornea with one of the fluorescent drugs, a form of superficial punctate keratitis was noted with the slitlamp. Scrapings of the epithelium, stained and examined microscopically, showed keratinization of the superficial epithelial cells. Such keratinized cells desquamate, leaving superficial punctate denuded areas which are made apparent by the stain. Such lesions, frequently seen when the cornea is exposed to a direct beam of radiation, always begin over the lower portion of the cornea, usually remain confined to this area, and may be present over long periods with no untoward consequences. The same process seems to take place in the bulbar conjunctiva, particularly over the lower portion.

Beginning about the third month and extending through the fifth, there may be some loss of cilia over the nasal portion of the lower lid and, to a lesser extent, the upper lid of the opposite eye. This loss may be replaced later by smaller, finer, and lighter eyelashes. After healing of the acute reaction and continuing over a period of several months to a year, there may be atrophy of the subcutaneous tissue of the skin of the bridge of the nose and the temple which has been exposed to the direct beam of radiation. In these same areas, the characteristic postradiation dryness and telangiectasis may occur later. In some instances, there may also be some keratinization or cornification of the lid margin extending past the gray line to or even beyond the posterior lid margin. These late changes in most of our cases have not been marked enough to constitute an unsightly blemish.

COMPLICATIONS

Extension of tumor into choroid. — Tumor growth, particularly in advanced cases, sometimes reaches the choroid and, in the rich vascular supply, grows rapidly, is uncontrolled by radiation, and eventually leads to metastasis. Clinically, the entrance of the growth into the choroid may be noted at first as a diffuse yellowish-white elevated area developing at one site along the border of, or encircling, the previously observed retinal lesion; or, in other cases, it may first appear adjacent to the disc. It continues to grow in extent and elevation until it is a large globular mass protruding into the vitreous, over the surface of which the retinal lesion may be identified.

From the study of pathological specimens, we have noted that the extension into the choroid may be at a site not only adjacent to the primary lesion but

FIG. 8 — CASE No. 10. *(a)* Right eye. The tumor in the retina has been reduced to foci of solid calcium scattered throughout a coagulation necrosis. Viable tumor tissue is present in the underlying choroid.

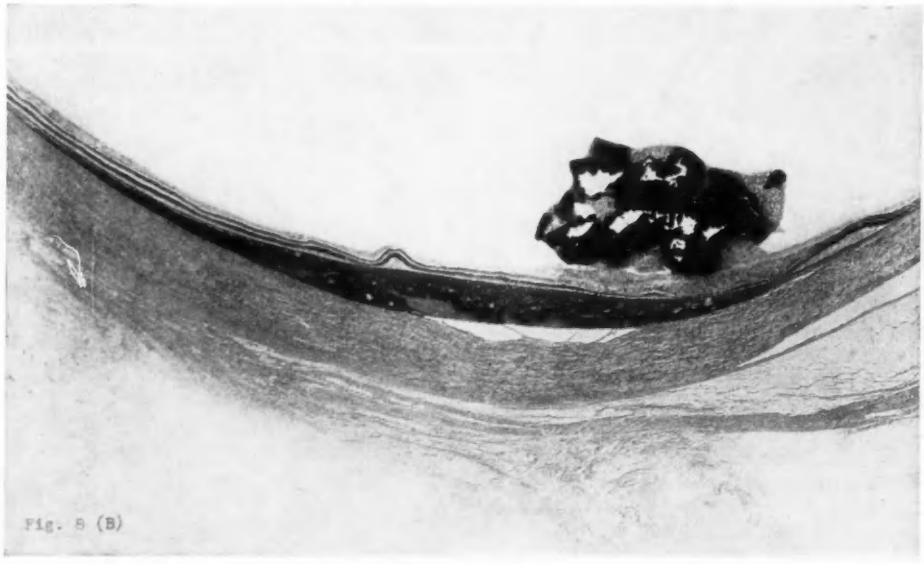


FIG. 8 *(b)* Left eye. The site of the tumor in the retina has been reduced to a mass of calcium lying in some coagulation necrosis. Underlying choroid shows viable tumor tissue with tendency toward perivascular growth.

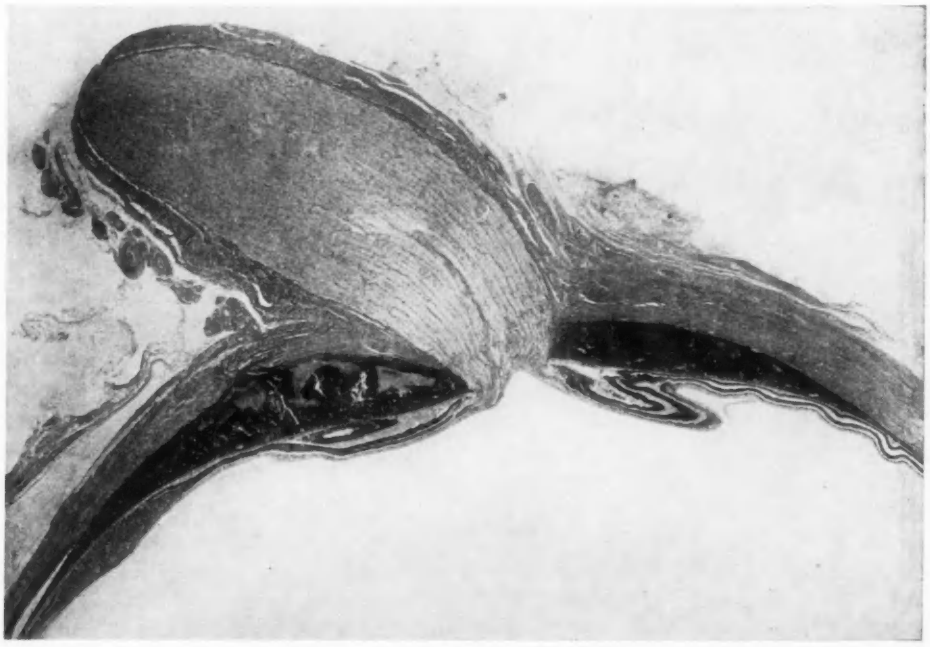


FIG. 8 *(c)* Left eye. Extension of the tumor to the choroid around the optic nerve. The underlying retina shows only one small focus of questionable viable tumor tissue.

also distal to it as a result of implantation growths along the internal choroidal surface. A common pathway of extension from the retina to the choroid is by way of termination of the lamina vitrea at the optic nerve along the border tissue into the choroid (figure 8c).

Radiation therapy seems to have very little if any effect on the growth when it has invaded the choroid. In both of the fatal cases in table III (cases 9 and 10), there was choroidal extension of the growth. In the first, it was noted clinically after six months and in the second after nine months of treatment (figures 8a, 8b, and 8c). A unilateral growth treated by radiation (table II, case 2), extended into the choroid and proved fatal (figure 2c).

Glaucoma. — From five to fifteen months following treatment, secondary glaucoma may develop. This complication was encountered in five cases (cases 1, 7, 8, 10, 11). The underlying changes which cause it are no clearer than those which occasionally produce secondary glaucoma in any eye which has been in the pathway of radiation. It is more often intractable than any other type of glaucoma; in our cases, repeated trephine operations and in one instance (case 11) an iridotasis operation were of no avail, and the eyes all became atrophic. In none of our cases did glaucoma develop where the treated lesion was small.

Cataract. — In five of the cases (cases 5, 6, 7, 8, and 11) cataract has been noted. Two of the five cases that appear to be arrested with well-functioning eyes have pure radiation cataracts. One appeared five years after treatment, is only a small dot in the posterior cortex away from the pupillary area, and does not in any way interfere with vision (figure 9). The other appeared three and a half years after treatment, progressed to maturity, and required a linear extraction. The other three of these five cases show no lens changes at the present time. In the other three cases cataracts developed after secondary glaucoma when the eye was proceeding toward atrophy. These cannot be classed as pure radiation cataracts as it is not clear to what extent they may have been due to the serious complications of the disease.

FIG. 9 — CASE No. 5 (H. F., January, 1941). This patient with bilateral retinoblastoma was first seen at Memorial Hospital in February, 1933. The right eye, in which the disease was more advanced, was enucleated and the remaining eye (left) was treated by radiation. She is now nine years old, with no evidence of disease, eight years after treatment. She wears a prosthesis on the right and has vision of 20/25 in the left eye. She has made normal progress in school and is now in the fourth grade.

Pannus formation. — In three cases (cases 7, 8, and 11), in which the growths were arrested permanently but in which the eye became atrophic, a superficial vascular membrane developed on the cornea after four to fifteen months. This complication began primarily at the limbus below and was noted first over the lower portion of the

cornea with later involvement of the entire structure, producing an unevenness of the corneal surface, a lack of lustre, and a diminution of transparency.

Detachment of the retina. — In an eye with multiple large retinoblastomas treated by a few massive doses of radiation at the Memorial Hospital some years ago and not included in the present series, a detachment of the retina developed following the disappearance of the tumor. Microscopic examination showed that this was due to the shortening of the retina through contracture of the scar tissue in it. The detachment, viewed ophthalmoscopically, gave a false appearance of progression of the tumor. So far, in the groups reported here, we have had no detachment of the retina. The chorioretinal adhesion over the site of the lesion tends to prevent it. As previously mentioned, an extension of the tumor into the choroid can be confused with a retinal detachment.

Atrophy of the globe. After two years, three of the globes treated (cases 7, 8, and 11) became atrophic and eventually phthisical. They were all rather advanced cases with multiple lesions in the retina and in eyes which obviously from the beginning did not tolerate the radiation well, as evidenced by the severe skin and conjunctival reaction, the development of dense pannus over the cornea, and the appearance of secondary glaucoma. The conjunctiva showed large telangiectatic vessels, and the cornea finally became completely opaque, vascularized, and shrunken. All of the conjunctiva and the corneal epithelium became keratinized and thus xerotic. This tendency to keratinization may be quite marked and may lead to the formation of large elevated masses of keratin on the cornea which eventually desquamates en masse, only to reform later. Finally, there may be some entropion of the lid margins, symblepharon, and a markedly contracted palpebral aperture.

Summary of complications following radiation. — In general, irradiation of the eye tends to keratinize the conjunctiva and corneal epithelium, the extent of which varies with the individual. Many of the above-mentioned complications represent only degrees of these processes. The sequence of the various stages are approximately as follows: superficial punctate keratitis, pannus formation, extension of the keratinized half of the lid margin over the gray line toward the conjunctiva, xerosis of the conjunctiva and cornea, and finally entropion of the lid margins, symblepharon, and contraction of the palpebral aperture. The complications can, in the main, be reduced to four more or less independent conditions: (1) keratinization of the conjunctiva and corneal epithelium and its sequelae as described above, (2) glaucoma, (3) cataract, and (4) choroidal extension. Whether or not keratinization and its sequelae assume serious proportions depends in some measure on the individual tolerance to radiation, a factor over which we have no control. Whether or not glaucoma develops seems to depend to a great extent on the size of the lesion treated and may be secondary to a uveitis from dissolution of tumor tissue. We have never encountered glaucoma as a complication following the treatment of small lesions. Whether or not cataract develops depends to some extent on individual susceptibility. In treating all types of lesions around the eye we have been impressed with the inconsistency between dosage given and subsequent lens changes. In any event, the most effective means of preventing serious eye complications is to make certain that the direct beam of radiation does not strike the lens, cornea, or conjunctiva.

TREATMENT OF RESIDUAL OR RECURRENT RETINOBLASTOMA IN THE ORBIT AFTER ENUCLEATION

The problem of radiation therapy in local postoperative recurrences of retinoblastoma in the orbit, or in cases where residual tumor has been left following operation, does not differ materially from that of other superficial growths. Since the eye has been removed, the eleborate precautions already described, the purpose of which is to conserve function in the treated eye, are not applicable, so that fractionated x-radiation should be given in heavy daily dosage over a period of three to four weeks rather than over several months, and this treatment, on completion, may be supplemented immediately by interstitial radon. The roentgen radiation is given through cylinders slightly larger (3 to 3.5 cm.) than those described in figure 3, at shorter target skin distance (35 to 50 cm.) and directed anterio-posteriorly. Over a period of three to four weeks, 7,000 to 9,000 r may be given, and immediately on the completion of this dose supplementary radon seeds (5 to 10 cm.) inserted. Such treatment brings on acute radiation effects in the skin and conjunctiva which, in the absence of the eye itself, are not particularly painful or distressing. Following such dosage (or even after 50 per cent as much), if the growth recurs after a period of several months, the treatment cannot be repeated without producing radio-necrosis, and therefore it is important to give the higher dose in the beginning in an attempt to sterilize the tumor in the orbit completely rather than to risk the recurrence of partially devitalized cancer a few months after a lesser dose. When such residual or recurrent cancer exists in an irradiated field, the radio-resistance of the partly devitalizcd cancer and of the normal tissues will be about equal so that the differential effect (greater radiosensitivity of cancer as compared to normal tissue) is no longer present, and radiation therapy is useless.

TREATMENT OF WIDELY DISSEMINATED RETINOBLASTOMA

The possible variations in the pallative treatment of individual patients with wide dissemination of retinoblastoma does not differ materially from that of any form of widely disseminated cancer. The principles and technic involved are too broad to come within the scope of this report.

END RESULTS

It is well-known that about 75 per cent of all cases of retinoblastoma are unilateral, and in these, enucleations are usually performed in the eye clinics where the patients are first seen, with permanent cures in 50 per cent of the cases. Such patients are seldom referred to a cancer clinic and in our series comprised less than 10 per cent of the total cases. Our series consists mainly of bilateral growths and cases in which the disease was far advanced, recurrent or residual in the nerve or orbit after operation. The percentage rate of cures of the entire group would therefore have little significance since it is not truly representative of retinoblastoma in general. For this reason we shall give the percentage end results only in Groups II and III. The one is made up of cases of bilateral tumors in which the vision had not been completely destroyed in the eye with the less advanced tumor and the patients were treated by enucleation of one eye and fractionated x-radiation to the other (Table VI), and the other is made up of residual or recurrent retinoblastoma (Table VII). Of the ten patients in Group II, eight are alive with apparent control of the disease. Of these, five have satisfactory vision over periods of 7, 6, 2½, 2 years, and 3 months respectively. In the latter case,

TABLE II UNILATERAL RETINOBLASTOMA (4 Cases)

CASE	AGE	First Seen Mem.Hosp.	CLINICAL FINDINGS	Period of Radiation	COURSE	GLAUCOMA	CATARACT	ENUCLEATION AND PATHOLOGIC FINDINGS	METASTASES	PRESENT STATUS	AUTOPSY FIN
RC No. 1	2½ Yrs.	Jan., 1936	OD—negative. OS—uniform, somewhat elevated involvement of entire retina; considerable vascularity; 1 mass, nasal and down, extends from most peripheral portion to posterior pole; no calcium; vascular. 1 mass, continuous with above, extends to vertical meridian, much less elevated, less vascular; calcium. Disc obscured by tumor tissue.	OS 6 mos.	Steady regression of lesion.	Apr. 1936—tension 15 Aug. 1936—tension 45 TREPHINE	Sept. 1936—No cataractous changes.	O.S. Oct., 1936. Path. Find. Entire retina detached and occupied by tumor which is necrotic below with calcium deposits and viable above with perivascular growth. Growths along choroidal surface. No extension into optic nerve. Some lens changes.	None	No evidence of disease 3½ years after radiation treatment.	
RW No. 2 (Fig. 2).	3 Yrs.	July, 1936	OS—negative. OD—large whitish growth involves entire globe except nasal superior portion.	OD 4 mos 11 days.	Regression of lesion for 2 mos. then detachment of retina, temporal half.	Dec. 1936—Acute glaucoma.	Dec., 1936—Lens cataractous.	O.D. Dec.,1936 Path.Find. Tumor fills choroid and ciliary body from iris to posterior pole; tumor cells extend through sclera; areas of necrosis in tumor mass; most of cells pyknotic; tendency to perivascular growth; retina detached over tumor but replaced at one area by new growth. Smaller tumor lesion in choroid near ora serrata on opposite side. No extension through nerve.	Mar., 1937, left parietal region; then left femur left frontal left zygoma left axilla right mandible left occipital right orbital socket right neck above regions received radiation.	Died 14 mos. after start of radiation treatment.	No evidence of ease; Generalized s metastases; Metastases to h liver, subcuta sue of thorax. Congestion of k spleen; X-ray films of show extensiv ment of pelvi tibiae and ea us.
VG No. 3 *	4 Yrs.	Feb., 1936	OS negative. OD—enucleated 4 mos. ago elsewhere. No evidence of local tumor. (See "metastases")	No radiation given to socket.	No evidence of local tumor.				Feb., 1936—Masses in right preauricular region, left superior orbital region extending into orbit with ptosis upper lid, bilateral enlargement of cervical lymph nodes, swelling of right arm and hand and left tibia. Above sites received radiation for 3 mos.	Died 7 mos. after enucleation and 3 mos. after start of radiation treatment.	Multiple meta bones and ce retroperitoneu nodes.
GG No. 4	4 Yrs.	Jan., 1931	OD—negative. OS—enucleation 2 wks. previously. Exenteration of orbital cavity shortly afterward.	Prophylatic radiation.	No evidence of local tumor.				None.	No evidence of disease 10 years after exenteration.	

*A case of distal metastases without local recurrence in orbit.

TABLE III
BILATERAL RETINOBLASTOMA TREATED BY FRACTIONATED OR DIVIDED DOSE PRINCIPLE OF ROENTGEN RADIAT
(10 Cases)

CASE	AGE	First Seen Mem. Hosp.	CLINICAL FINDINGS	Period of Radiation	COURSE	GLAUCOMA	CATARACT	Enucleation and Pathologic Findings of Eyes Receiving Radiation	METASTASIS	PRESENT STATUS	AUTOPS FINDIN
H F No. 5 (Fig. 9)	9 mos.	Feb., 1933	OD—enucleation July, 1932 elsewhere with no implant Path. Find.: Retinoblastoma. OS mass in macular region extending to disc 8-9 D elevation.	OS 16 mos.	Steady regression of lesion.	Not present.	May, 1938—Very small localized opacity posterior lens cortex temporally. No progression to November, 1940.		None.	Lesion arrested; vision 20/25; good general health; attends regular school (Fig. 9).	
L C No. 6	5 Yrs.	Aug., 1933	OS enucleation with no implant. Path. Find. Retinoblastoma. OD at equator, from 3-5 o'clock, 7-8 D elevation; 4 DD across.	OD 20 mos.	Steady regression of lesion.	Not present.	Jan., 1937—Posterior polar opacity which progressed until Feb., 1940 when, vision being 20/200 needling was done which was followed 1 wk later by linear extraction.		None.	Lesion arrested, vision 20/100-1 (reduced vision due to macular changes secondary to either growth or radiation); good general health; attends school.	
A G No. 7	14 mos.	Dec., 1934	OX enucleation with no implant. Path. Find. Retinoblastoma. OD 1 mass at nasal disc margin peripherally 3 DD, 5 D elevation, surface blood vessels 1 mass, small budlike directly above.	OD 15 mos.	Steady regression of lesion seen as long as interior of eye could be observed.	Jan., 1936, OD—Secondary glaucoma with steamy cornea; also vascularized pannus; TREPHINE; Apr., 1936—Tension 50-TREPHINE.	Sept., 1936—Lens completely cataractous.		None.	Lesion arrested, but globe is shrunken; small vascularized cornea; xerotic conjunctiva; some symblepharon; Blind but in good general health.	

NOBLASTOMA (4 Cases)

ATARACT	ENUCLEATION AND PATHOLOGIC FINDINGS	METASTASES	PRESENT STATUS	AUTOPSY FINDINGS
936—No cataract-hanges.	O.S. Oct., 1936. Path. Find. Entire retina detached and occupied by tumor which is necrotic below with calcium deposits and viable above with perivascular growth. Growths along choroidal surface. No extension into optic nerve. Some lens changes.	None	No evidence of disease 3½ years after radiation treatment.	
1936—Lens cata-is.	O.D. Dec.,1936 Path.Find. Tumor fills choroid and ciliary body from iris to posterior pole; tumor cells extend through sclera; areas of necrosis in tumor mass; most of cells pyknotic; tendency to perivascular growth; retina detached over tumor but replaced at one area by new growth. Smaller tumor lesion in choroid near ora serrata on opposite side. No extension through nerve.	Mar., 1937, left parietal region; then left femur left frontal left zygoma left axilla right mandible left occipital right orbital socket right neck above regions received radiation.	Died 14 mos. after start of radiation treatment.	No evidence of local disease; Generalized superiosteal metastases; Metastases to hilar nodes, liver, subcutaneous tissue of thorax; Congestion of kidneys and spleen; X-ray films of skeleton show extensive involvement of pelvis, femora, tibiae and each humerus.
		Feb., 1936—Masses in right preauricular region, left superior orbital region extending into orbit with ptosis upper lid, bilateral enlargement of cervical lymph nodes, swelling of right arm and hand and left tibia. Above sites received radiation for 3 mos.	Died 7 mos. after enucleation and 3 mos. after start of radiation treatment.	Multiple metastases to bones and cervical and retroperitoneal lymph nodes.
		None.	No evidence of disease 10 years after exenteration.	

III
OR DIVIDED DOSE PRINCIPLE OF ROENTGEN RADIATION
es)

ATARACT	Enucleation and Pathologic Findings of Eyes Receiving Radiation	METASTASIS	PRESENT STATUS	AUTOPSY FINDINGS
1938—Very small zed opacity poster-ns cortex tempor-No progression to mber, 1940.		None.	Lesion arrested; vision 20/25; good general health; attends regular school (Fig. 9).	
937—Posterior po pacity which pro-d until Feb., 1940 vision being 20/ needling was done was followed 1 wk by linear extrac-		None.	Lesion arrested, vision 20/100-1 (reduced vision due to macular changes secondary to either growth or radiation); good general health; attends school.	
1936—Lens com-y cataractous.		None.	Lesion arrested, but globe is shrunken; small vascularized cornea; xerotic conjunctiva; some symblepharon; Blind but in good general health.	

TABLE I

CASE	AGE	First Seen Mem. Hosp.	CLINICAL FINDINGS	Period of Radiation	COURSE	GLAUCOMA
E A No. 8	11 mos.	Mar., 1935	OD 1 mass in macular region, 4 D elevation, surface blood vessels; 1 mass nasally above horizontal meridian. OS buphthalmic, vitreous filled with mass, surface blood vessels, tension 48.	OD 15 mos. OS 3 mos.	OD steady regression of lesion seen as long as interior of eye could be seen. OS after 2 wks, hyphaemia 2 mos., globe atrophic	June, 1936, OD—Secondary glaucoma with steamy cornea; also vascularized pannus; Aug., 1936—Tension 35 TREPHINE. Nov., 1936—Tension 50 TREPHINE.
B L No. 9	17 mos.	May, 1935	OD 1 large bullous mass below disc, surface blood vessels; 1 small nodule 4 DD temporal to disc. OS enucleation, with no implant. Path. Find. Retinoblastoma.	OD 14 mos.	Regression satisfactory for 5 mos., then lesion below disc increased in size, first concealing the disc, then spreading into and under the retina; after 1½ years' treatment most of vitreous cavity occupied. Implantation growths on iris. It was thought that the tumor had invaded the choroid.	Not present.
R O No. 10 (Fig. 8)	10 mos.	Sept., 1935	OD 1 mass nasal to disc, horizontal meridian 4 DD in size, 4 D elevation, surface blood vessels; 1 mass half-size directly below; tension 35. OS 1 mass macular region from disc margin to periphery, 6 D elevation; surface blood vessels; 1 mass nasally horizontal meridian 2 DD in size; tension 30.	OD, 8 mos. OS, 8 mos.	OD—Steady regression of lesion. OS—Regression satisfactory for 7 mos. then retina appeared detached around site of temporal lesion; gradually more elevated and bullous-like with tumor area mounted on its surface. It was thought that the tumor had invaded the choroid..	May, 1936 — Secondary glaucoma.
J E No. 11	3 mos.	Oct., 1937	OD 1 mass nasal to and above disc 2-3 DD wide, 2 D high, one surface blood vessel; 1 mass (smaller) temporally above macula. OS enucleation with no implant. Path. Find.: Retinoblastoma.	OD, 5 mos.	OD—Steady regression of lesion as long as interior of eye could be seen (4½ mos.); then pannus of cornea and corneal vascularization developed.	OD—Secondary glaucoma, Mar., 1939, TREPHINE Mar., 1940, TREPHINE May, 1940, IRIDOTASIS
D S No. 12	2 mos.	June, 1938	OD enucleation with no implant. Path. Find.: Retinoblastoma. OS temporally, horizontal meridian, 3-4 DD from disc mass 3x4 DD, 4 D high.	OS 2½ mos.	Complete disappearance of tumor; only some calcium granules remain.	Not present.
E B No. 13 (Fig. 7)	3 Yrs.	June, 1939	OD enucleation with no implant. Path. Find.: Retinoblastoma. OS peripherally, nasal, on horizontal meridian, from near equator to limit of visibility; surface vessels.	OS 4 mos.	OS—Steady regression.	Not present.
P O No. 14	3 Yrs.	May, 1940	OD tumor mass occupies entire nasal portion of fundus. OS enucleated without implant Path. Find.: Retinoblastoma.	OD, 4 mos.	Steady regression of tumor for 4 mos.	Not present.

III—Continued

CATARACT	Enucleation and Pathologic Findings of Eyes Receiving Radiation	METASTASIS	PRESENT STATUS	AUTOPSY FINDINGS
Jan., 1937—Lens cataractous.	OS, 1935—Path. Find.: Globe phthisical; retinal elements not recognizable; vitreous partially filled with necrotic tumor tissue containing many foci of calcium. No extension into nerve or through sclera.	Mar., 1937 4 cm avoid mass subcutaneous tissue right submaxillary region. Complete regression after x-radiation.	OD—Tumor arrested but globe phthisical; xerotic conjunctiva and unusual piling up of keratin on cornea in form of conical protuberance between palpebral aperatures for 10-12 mm. which finally falls off only to accumulate again. Blind, but in good general health.	
No cataractous changes.		Unknown.	Died 1 yr. 10 mos. after first seen and treatment started.	Autopsy not obtained.
No cataractous changes.	OS, June, 1936—Micro. Find.: Retina detached; on temporal side replaced by necrotic tumor tissue with calcium foci; small areas viable tumor about blood vessels; extension of tumor into nerve for short distance posterior to lamina cribrosa but operative section free; no extension through sclera many implantation growths on choroid. On temporal side, beneath primary retinal site, flat extension of tumor into choroid from disc to point past equator, actively growing.	Oct., 1936—Mass left orbit, RADIATED; x-ray films show left ethmoid, nasal wall and floor of orbit extensively involved; bones of skeleton not involved. Later—Mass left side hard palate and mandible. Later—Right and left cervical glands palpable.	Died 1 yr. 10 mos. after first seen.	Recurrent retinoblastoma left orbit with extension to nasal cavity and bones, to right maxilla and mandible and adjacent bones, to cranial cavity via nasal cavity and cribriform lamina and to opposite orbit from nasal cavity. OD—In retina, nasal to disc, slightly above horizontal meridian, 4 DD away, mass 2-3 DD wide, 1½ DD high; mostly dense, solid calcium and necrotic tissue with clear areas of absorption. Flat tumor in choroid beneath retinal lesion, extending to disc and several DD around it. Choroidal tumor extended through posterior emissaria to external scleral surface; tumor cells identifiable as far anteriorly as limbus; tumor in nerve head but not as far as lamina cribrosa.
Lens became cataractous after atrophy of globe.		None.	OD tumor arrested but cornea completely opaque with marked vascularity; xerosis of cornea and conjunctiva. Blind but in good general health.	
No lens changes.		None.	Apparently normal vision and in good general health.	
No lens changes.		None.	OS—tumor arrested; vision 20/20; in good general health.	
No lens changes.		None.	OD tumor appears arrested. Vision—counts fingers at 20 feet.	

TABLE I

CASE REPORTS

Because of incomplete histories, the cases of patients treated between 1916 and 1929, inclusive, are summarized briefly in Table I. Individual case histories of patients treated between 1930 and 1940 inclusive, are given in Tables II, III, IV and V.

Cases of Reinoblastoma Treated at the Memorial Hospital for the Treatment of Cancer and Allied Diseases, 1916-1929, inclusive.

	No. of Cases	M	F	OS	OD	*Treatment* Rad.	Enuc.	Comb.	Cataract	Glaucoma	Metastasis	Outcome*
Group I												
Primary, Unilateral	7	3	4	2	5		1	6		1	1	1 DOD 2 NED 2 L with D 2 L no D
Group II												
Bilateral	16	8	8			4		12	1		3	8 DOD 2 NED 5 L with D 1 L no D
Group III												
Recurrence after enucleation	5	2	3	3	2	4		1			5	4 DOD 1 L with D
Group IV												
Residual after enucleation	3	1	2	3		3					1	1 DOD 2 L no D

* DOD — Dead of disease; NED — No evidence of disease; L with D — Lost with disease; L no D — Lost with no disease present.

the treatment has only recently been completed, but the growth is apparently satisfactorily controlled. The other three patients are alive, the disease under control, but with no vision in the treated eye. Two are dead of disease. Of the seven cases in Group III, the four with recurrent tumor in the orbit are dead of disease. Of the three cases with residual tumor in the orbit, two are living and well with no evidence of disease, and one is dead of disease. If we combine the residual and recurrent cases in 1916 to 1929 (Table I) with those in 1930 to 1940 (Table VII), it will be seen that there are a total of six cases of residual tumor left in the nerve at the time of enucleation with only one patient dead of disease and five apparently living and well. There are nine cases of recurrent tumor in the orbit after enucleation, all of which are dead. These figures would indicate that if it is seen immediately after enucleation that

TABLE VI

Memorial Hospital for the Treatment of Cancer and Allied Diseases

END RESULTS IN TREATMENT OF BILATERAL RETINOBLASTOMA
1930-1940 Inclusive

Bilateral retinoblastoma treated by enucleation of one eye and fractionated irradiation of the other:

Total number of cases	10
Alive and well	8 (80%)
With vision	5 (50%)
Without vision	3
Dead of disease	2

TABLE VII

Memorial Hospital for the Treatment of Cancer and Allied Diseases

END RESULTS IN THE TREATMENT OF RESIDUAL AND RECURRENT RETINOBLASTOMA
1930-1940 Inclusive

Total number of cases	7
Residual:	
Living and well	2
Dead	1
Recurrent	
All dead	4

Table IV — RECURRENT OR RESIDUAL RETINOBLASTOMA IN ORBIT AFTER ENUCLEATION TREATED WITH IRRADIATION (7 Cases)

CASE	AGE	ENUCLEATION	RECURRENCE or RESIDUAL TUMOR IN ORBIT	COURSE FOLLOWING IRRADIATION	METASTASIS*	OUTCOME	AUTOPSY FINDINGS
E B No. 15	3½ Yrs.	OD with glass ball implant.	Evident after 3½ mos.	Disappearance of tumor in orbit.	4 mos. later—pain in both legs and chain of small nodes palpable in right cervical region; x-ray films show involvement of shaft both humeri, upper end right fibula and tibia and each scapula.	Died 1 yr. after enucleation and 9½ mos. after recurrence and beginning of treatment.	Metastasis to pancreatic nodes, acute interstitial pancreatitis; extension of tumor into chiasm and left optic nerve; renal metastasis; epicardial hemorrhafic area fails to show tumor in section but a metastasis probably present nearly occluding a vessel.
H J No. 16	5 Yrs.	OS—with no implant. Path. Find.: Entire globe filled with tumor; *rupture through limbus with growth along external scleral surface* almost to equator; choroid invaded everywhere except for short distance at equator; optic nerve invaded to lamina cribrosa; no invasion thru emissaria.	Evident after 5 mos.; also numerous soft freely movable nodes palpable in cervical region, especially left side; 1 large node beneath angle of right mandible.	Complete regression.	See note under "RECURRENCE IN ORBIT."	No evidence of disease 1 yr. 9 mos. after enucleation and 14 mos. after recurrence.	
A B No. 17	2½ Yrs.	OS—with no implant. Path. Find.: Extensive lesion invading optic nerve, completely replacing nerve tissue and extending into intervaginal space; choroidal extension; *operative section not free of tumor tissue.*	Evident after 3 weeks.	Disappearance of mass in orbit.	2 mos. later—headache, listless, vomiting; OD appeared blind. 1 mo. later—coma, convulsions.	Died 5 mos. after enucleation and 4 mos. after recurrence noted.	Invasion of brain with tumor, internal hydrocephalus, subperiosteal metastasis to calvarium.
R K No. 18	17 mos.	O S—with no implant.	1 mo. (case referred for prophylactic radiation). 2 mos. later—firm mass palpable in orbit.	Disappearance of mass.	4 mos. later—pain in back and walking difficult. Prominence over left sacral region (x-ray films show bone destruction. Later—firm nodules in frontal bone, both temporal bones, left maxilla, molar processes; loss of pain sence below midthigh, weakness right arm; x-ray films show involvement of body of 9th dorsal vertebra, skull and upper 3/4 right humerus; blood in stools, convulsions.	Died 1 yr. after enucleation and 9 mos. after recurrence was noted.	Metastatic retinoblastoma in brain, vertebra, skull and kidneys; bronchopneumonia and pyelonephritis. OD—not remarkable except for metastatic nodule in episclera and external scleral layers at nasal limbus; no tumor foci in retina.
J P No. 19	18 mos.	OS—with no implant.	Evident after 4 mos., given local treatment elsewhere for 3 mos. then referred to Mem. H. 4-5 cm. mass in orbit adherent to lids and surrounding bones; biopsy showed a hematoma within lesion.	Mass regressed to 4/5ths original size; residual tissue thought to be organized disintegrated tumor tissue.	2 mos. later—hard mass 2½ cm near external occipital protuberance and pea-sized mass left parietal region. 1 mo. later—nodule left mandible, then left shoulder, lower left humerous, and left lower alveolus.	Died 1 yr. 1 mo. after enucleation and 8 mos. after recurrence first noted.	Metastasis to skull, 5th right rib, 5th, 6th, 7th left ribs, left humerus, right femur, right tibia, left radius; bilateral deep inguinal and femoral nodes, pancreas; miliary parenchymatous abscesses right lower and upper lobes of lungs.

*All these cases received irradiation to the metastatic sites.

TABLE IV—Continued

CASE	AGE	ENUCLEATION	RECURRENCE or RESIDUAL TUMOR IN ORBIT	COURSE FOLLOWING IRRADIATION	METASTASIS*	OUTCOME	AUTOPSY FINDINGS
P B No 20	2 yrs.	OD enucleated (no implant). OS radiated elsewhere for 6 mos. (marked regression claimed). To Mem. Hosp. after 4 mos.—*right orbit* filled with mass; *left eye*—retina completely detached and vascular mass nasally, almost to posterior lens surafce. OS enucleated. Path. Find.: Retinoblastoma, no invasion optic nerve or emissaria. OD orbit exenterated and 5 gold-filtered radium seeds implanted in stump of optic nerve about inferior orbital fissure.	Evident after 4 mos. in right orbit.	8 days post-operatively, temperature 104°; vomiting, ankle jerks hyperactive, hyperaesthesia over entire back; considerable purulent discharge from left orbit. Patient became comatose with marked retraction of neck.		Died 3 weeks post-operatively; clinical diagnosis—meningitis from implantation of seeds in optic nerve.	Acute diffuse fibrinopurulent meningitis and bronchopneumonia. No residual tumor noted.
W H No. 21	4 yrs.	OS enucleation; no implant. Path. Find.: Entire vitreous filled with tumor which contains large areas of necrosis; *extension through sclera*; optic nerve invaded but operative section appears free.	Evident at time of enucleation as a whitish, semicaseous, friable tissue posterior to the globe.	Disappearance of tumor in orbit.		No evidence of disease 2½ yrs. after enucleation and irradiation.	

* All these cases received irradiation to the metastatic sites.

Table V — FAR-ADVANCED BILATERAL RETINOBLASTOMA (2 Cases)

CASE	AGE	FIRST SEEN MEM. HOSP.	CLINICAL FINDINGS	TREATMENT	COURSE	METASTASES	OUTCOME	AUTOPSY FINDINGS
J R No. 22 (Fig. 1)	3 yrs.	Oct., 1938	OD vision completely destroyed by growth. OS light perception only. Growths so far advanced no treatment was advised.	None.	Oct., 1939—Readmitted for terminal care. Blind. Both eyes protrude. Exophthalmus increased and OD enucleated Dec., 1939, and OS in Feb., 1940 for palliative reasons.	Nov., 1939—Mass in right preauricular region. Later: in neck—right " groin " " thoracic cavity " scalp. X-ray films show: Extensive osteolytic lesions of humerus, femora, bony pelvis, and mass in middle left chest.	Feb., 1940—Died of disease.	Direct extension into brain; Lymph node metastases (generalized) including cervical, axillary epitrochlear, aortic, iliac, inguinal (all bilateral) and abdominal; Every bone involved except hands and feet (mostly subperiosteal Both testicles completereplaced by tumor tissue; No subcutaneous metastases.
P D No. 23	1½ yrs.	July, 1940	OD—retina completely detached, filled with multiple tumor foci. Calcium present. Tension: 35. OS—same as in OD except more advanced. Tension: 50.	July, 1940—bilateral enucleation. (Specimens preserved intact; no microscopic report).	No evidence of disease.	None.	Dec., 1940—no evidence of disease. General health good.	

residual tumor has been left in the optic nerve, the patient has over an 80 per cent chance of recovery with immediate irradiation, and that if such residual tumor is not known and is detected only when it appears as a recurrence, then the situation is hopeless.

SUMMARY

A detailed report is made of 23 cases of retinoblastoma which were referred to the Memorial Hospital for the Treatment of Cancer and Allied Diseases during the years 1930 to 1940 inclusive. This series does not represent retinoblastoma in general since the majority of the patients were referred because of advanced or bilateral tumors. The selection of the method of treatment for retinoblastoma is discussed, and technics of the various types of treatment are described. The main purpose of this report is to discuss a method of treatment for bilateral retinoblastoma which consists of enucleation of the eye in which the disease is more advanced and radiation therapy to the other in an attempt to control the disease and conserve vision. The technic of such radiation therapy is described in detail. The series of ten cases includes eight successful ones with satisfactory vision in five after 7, 6, 2¼, 2 years, and 3 months respectively. Pathological findings are given in detail only of eyes enucleated after receiving radiation.

REFERENCES

1. Martin, H. E., and Reese, A. B.: Treatment of Retinal Gliomas by the Fractionated or Divided Dose Principle of Roentgen Radiation. Arch. Ophth. 16:733-761, 1936.
2. Pfeiffer, R. L.: Roentgenographic Diagnosis of Retinoblastoma. Arch. Ophth. 15:811-821, 1936.

DISCUSSION

MARY K. ASBURY, M.D., Cincinnati: The results of the excellent study just presented will be helpful to all ophthalmologists. Few have the opportunity to observe and follow a large number of cases of this relatively rare clinical entity. In this paper have been reviewed the effects of radiation therapy in nine cases of bilateral retinoblastoma, twelve cases of recurrence of retinoblastoma in the orbit after enucleation, and five cases in which tumor tissue was left behind in the orbit at operation — twenty-six cases in all. At the Holmes Laboratory specimens from only three cases of retinoblastoma have been received during a period of time comparable to that covered by this study. The lesions were unilateral in two cases and bilateral in one. In reviewing these cases it was found that radiation therapy had been used in only one, the bilateral case, because of the extent of the lesions. Certainly no conclusions can be drawn from such a limited series; however, it represents the collected cases of several ophthalmologists.

To my mind, this study strengthens the opinion that enucleation of both eyes is the safest procedure in cases of bilateral retinoblastoma if more than a small part of the retina is involved in the second eye. Natural sentiment is against bilateral enucleation in young patients, in whom retinoblastoma invariably occurs, but the cases just reported indicate that this disaster does not preclude normal life. The first case of bilateral retinoblastoma which I was privileged to see illustrates this point, as well as the favorable effect of radiation on small lesions. The patient was the famous twin whom Doctor Benedict treated. One eye was enucleated, and the diagnosis of retinoblastoma was confirmed microscopically. A small lesion in the other eye was treated with radium, and sight was preserved for a time. Fifteen years later the patient had married and had a healthy baby seven months old. Several years before her marriage, the remaining eye had been enucleated.

The results obtained by Doctor Reese and Doctor Martin by radiating recurrent orbital lesions are very discouraging, and apparently metastases are as hopeless as ever. The best procedure seems to be immediate radiation after enucleation, especially if there is a possibility that tumor cells have been left behind in the orbit. The case of bilateral retinoblastoma, previously referred to, in which double enucleation was carried out followed by radiation, responded favorably. The patient is living and well more than three years after operation. Microscopically, the right eye showed no evidence of secondary glaucoma nor extension of the tumor into the optic nerve, although all but the anterior edge of the retina had been replaced by tumor tissue,

and the vitreous cavity was practically filled by the neoplasm. In the left eye more of the retinal tissue had been spared, but tumor cells had invaded the choroid near the posterior pole and were also found in the optic nerve behind the lamina cribrosa.

In the past, finding tumor cells in the optic nerve in a case of retinoblastoma was considered equivalent to a death warrant. The prompt use of radiation in suitable dosage offers hope of cure in this type of case, and the clinician is urged to make use of this valuable therapeutic adjunct.

K. L. Stoll, M.D., Cincinnati: Doctor Martin and Doctor Reese's paper furnishes valuable information for which I am very grateful. A few remarks regarding the case of bilateral intraocular retinoblastoma, referred to by Doctor Mary K. Asbury, may be in order.

On May 8, 1937, a patient, aged 27 months, was referred to me with a history of failing vision which had been noticed in the fall of 1936. Soon afterwards a "yellowish glare" appeared in the pupils. The eyes had deviated upward and converged during the preceding six months. There was no history of serious ocular disturbance in the family of either parent. Examination revealed the pupils to be moderately enlarged and of a bright yellow-gray hue. The right pupil reacted faintly. The right anterior chamber was of nearly normal depth; the left was very shallow so that the iris practically touched the cornea. The lens was clear in each eye. Tumor masses, presenting uneven surfaces, were observed adjacent to the posterior capsules of the lenses. These masses filled the vitreous chambers, leaving only narrow spaces above. The surface of the tumor in the left eye was covered by numerous newly formed blood vessels. The eyeballs were slightly congested, and the intraocular tension appeared normal on palpation.

A week afterwards, on May 14, 1937, both eyes were enucleated, and liberal portions of the optic nerves were resected. The cross section of the right optic nerve appeared white; that of the left faintly pink. Histologic examination, which was done by Dr. Mary K. Asbury, revealed normal findings in the cross sections of both optic nerves. The patient made an uneventful recovery and was discharged from the hospital on May 16, 1937.

Postoperative administration of x-ray therapy, intended prophylactically, was delayed when the child contracted measles. There was no interference, however, with prompt healing of the sockets.

Dr. Sidney Lange, of Cincinnati, administered five x-ray treatments, postoperatively, to each orbit between June 5, 1937, and June 30, 1937. At the time of each treatment a dosage of 200 r units was given to each orbit. Both orbits, therefore, received 1,000 r units. The voltage used was 200,000 with filtration of 1 mm. of copper, at a distance of 60 cm. There were no ill effects following radiation except edema and a slightly blood-tinged discharge from the left orbit, which continued from June 19 to June 26, 1937.

When the patient returned July 31, 1937, the sockets were free from congestion and edema, and protheses could be fitted. No adverse symptoms were noted two and three years later, when new protheses were fitted. The child is developing well physically and mentally.

It is gratifying to state that no recurrence has developed up to this date which is three years and four months after enucleation. The hope appears to be justified, therefore, that a permanent cure has been obtained as a result of postoperative radiation.

E. H. Cary, M.D., Dallas: Doctor Reese's report is very interesting, and I believe that I have something to add which relates to two cases that I reported in a paper in 1931 at the meeting in Detroit of the American Medical Association. This paper included a thorough study of the subject of tumors of the orbit and a survey of many cases that I had treated.

In 1903, I examined a child six months old in whom both eyes were affected. The anterior chambers were practically annihilated, and the diagnosis could be made very readily. In those days retinoblastoma was called glioma. The mother would not consent to enucleation, and I could suggest nothing else except x-ray. I reasoned that perhaps the administration of x-ray therapy for a few weeks' period would prove beneficial. The treatments were given with the old static machine of that day, and the radiation was a very mild form in all probability. Radiation was given for 15 minutes every other day for a period of six weeks, alternating the exposure so that each eye was treated every fourth day. This method was similar to the Cutard method of today.

I did not see the child again until eight years afterwards, at which time examination revealed that both lenses were calcareous, but there was light projection for a part of each field. When I removed the lens in one eye, I found a cyclitic membrane which was obscuring the vision and causing retardation

of light into the eye. I split the membrane, following which the child was able to see on the side where the retina was not involved and was not detached. Later, I carried out the same procedure in the other eye, following which there was vision for objects.

I lost track of the patient for a long time, but after a while he came to see me. He was then living in an adjoining city. He is still alive, and in one eye he now sees light and form.

My next case may be interesting, from the prognostic standpoint, as an adjunct to Doctor Reese's report. The patient was a lad in whom the golden reflex had been noticed by his family for a period of ten months. The family physician was consulted, and it was his opinion that the child had a cataract. He referred the patient to me. The condition was easily recognized, and I made a diagnosis of retinoblastoma. The section revealed invasion of the optic nerve, and at the time, I believed that this would lead to an early recurrence. After the eye had been enucleated, radiation was administered. This patient was treated over ten years ago, and he is still living and well.

WILLIAM E. BORLEY, M.D., San Francisco: This presentation of cases of retinoblastoma by Doctor Martin and Doctor Reese is of great value to those of us occasionally faced with this grave disease. The pessimistic attitude of ophthalmologists toward the treatment and the prognosis of retinoblastoma can easily be understood if one reviews the many isolated reports of failures which have resulted from all types of therapy.

I would like to commend the authors for their diligence in pursuing this study and for the time and patience it must have involved in the frequent observation and treatment of these children over many months and years. I think the main lesson to be learned from all this is that we should send our cases to Doctor Martin and Doctor Reese.

The successful outcomes in such a large number of cases reveals to me the importance of standardized technics when used at an institution such as the Memorial Hospital, where experience broadens much more rapidly than is possible in smaller hospitals in less populated areas, and I feel that those of us who rarely come in contact with this condition should make every effort to send our cases to such an institution.

I do believe, however, that each individual's experience in treating the various forms of this neoplasm may add something of value to the sum total of knowledge regarding it, and for this reason I would like to present briefly the following case reported by Doctor Hans Barken, of the Eye Service at Stanford University Hospital. This was reported in 1933, at which time the result was not final.

Keeping in mind the desirability of exposing the tumor to a maximum of radiation with a minimum of exposure of the skin, lens, retina, and orbital tissues, we endeavored to treat an infant affected with bilateral glioma which was well advanced in one eye and early in the other. The eye with the advanced tumor was removed, and the diagnosis was confirmed by sections. In the macular area of the remaining eye was situated a tumor about four disc diameters across and elevated about 3 to 4 diopters.

(Slide.) This is an artist's drawing of the tumor in the macular area. The treatment of this eye consisted of the application of two radium seeds, each containing five milligrams, enclosed in a stent of wax which was molded so that it would closely fit the scleral curve on the temporal side of the eyeball.

(Slide.) The embedded seeds are shown here. At one end there is a small hook which is intended to hook over the optic nerve, if possible, and at the other end is a device for inserting the suture of fine wire so that the radium can be removed readily.

This was slipped into position after an incision was made through the conjunctiva and Tenon's capsule and after a tenotomy of the lateral rectus muscle was carried out. In this way, the radium was very close to the actual tumor tissue; in fact, it was not more than one centimeter from the free surface of the growth. At least, that was the intended placement.

(Slide.) The treatment was administered on two occasions with a three months' interval, and each dose was equivalent to 400 milligram hours. This approximated 20,000 roentgen units at the scleral surface, or about 2,500 roentgen units at the free edge of the tumor, provided the stent was exactly over the tumor in proper position. We could not be sure of this, however. At the time this procedure was attempted, which was during the days when a great deal was not known about retinal localization, one could not be positive of the exact area from the surface.

Although there was some regression of the growth at first following both treatments, the tumor progressed rapidly in about a year. In spite of enucleation of the eye, the child died of intracranial extension.

(Slide.) The tumor is shown here several months after the last treatment. Small addi-

tional tumors can be seen, and one is located at the nasal side of the disc. Finally, extension occurred below, although a great part of this growth was made up of freely movable, detached retina from above.

The method seems plausible to me in the case of a well localized and easily accessible lesion in a remaining eye, as compared with a large number of divided doses administered through the skin and orbital structures. In using the former method there should not be much danger to the eye, especially to the anterior segment.

With the advanced technics for retinal localization, the area to be treated can be localized with accuracy on the scleral surface, provided the tumor is small.

I have in mind projection of light from an ophthalmoscope through the sclera and along the borders of the tumor. Marking can be made with either diathermy or gentian violet, and then the areas within these marks can be treated.

Doctor Newell of our Radiology Department believes that one or two doses administered in this manner is equivalent to the total effective irradiation of divided doses over a long period of time.

I realize that the majority of retinoblastomas are far too extensive to be treated by such a method, but I would appreciate Doctor Reese's opinion regarding such a procedure in the treatment of a very small, easily localized glioma in a remaining eye.

ALGERNON B. REESE, M.D., New York: Recently I enucleated both eyes of a patient with bilateral retinoblastoma. In this patient the disease was far advanced in both eyes, and we felt that radiation was not indicated. We are convinced that if the tumor mass is very large, its dissolution by radiation in the confined intraocular space is more than an eye can tolerate and will frequently lead to secondary glaucoma and eventually atrophy of the eye.

Fortunately, however, in most cases of bilateral retinoblastoma the disease is far advanced in only one eye and in a very early stage in the other. Furthermore, parents are appalled at the idea of bilateral enucleation and, in our experience, frequently will not give permission for the enucleation of both eyes even when it is indicated. For these two reasons bilateral cases are usually suitable for radiation, and I cannot agree with Doctor Asbury that as a rule bilateral enucleation is indicated.

I wish to emphasize that there is very little difficulty in curing or arresting retinoblastoma by radiation. The problem is not merely to arrest the process, but to arrest it and leave the patient with a well-functioning eye. I should like to repeat that four of our cases have good vision.

I did not mention our recurrent cases. I agree with Doctor Asbury that they are very discouraging. Ten cases with the orbit more or less filled with recurrent tumor have been treated. Of these ten we have one which is now apparently arrested, one year and seven months after the completion of treatment. Nine have died.

It was very interesting to hear Doctor Stoll's report.

Doctor Cary is to be congratulated on arresting the disease in his case, but my understanding is that the patient had very little vision. As I have said before, we can be fairly certain of curing the disease in the eye. Our problem is to destroy the tumor and not destroy the function of the eye. Otherwise, bilateral enucleation would be preferable.

I appreciate very much Doctor Borley's remarks. I am not qualified to discuss the radiation factors but the principle he advocates appeals to me, and I hope he will pursue it further and give us a report later.

MALIGNANT MELANOMAS OF THE EYE AND ADNEXAE

DON MARSHALL, M.D.
KALAMAZOO, MICHIGAN

ALMOST any pigmented lesion in or about the eye, excepting those deposits that follow inflammatory and certain degenerative processes, is a potential malignant melanoma. The presence of pigment is a normal characteristic both inside and outside the eye, and malignancy from some pigmented tissue is rare; but the potential fatal issue of most abnormal pigmented lesions of the eye is so great and the malignancy in them is so stubborn and so difficult to handle that a review of this group of tumors may be of some value.

Investigations and research during the last two decades have developed a completely new conception of the etiology of both intraocular and extraocular melanomas. It has been shown that pigment cells are of ectoblastic origin. Also, Masson,[13] of Montreal, has shown in an important basic research that all types of sensory and motor neural tumors have as a fundamental element a proliferation of cells of the nerve sheath of Schwann and are therefore ectodermal in origin. Such a peripheral neural tumor develops independently of connective tissue. Neurofibromas, various types of neuromas, neurogenic sarcomas, and nevi are a closely allied group. All of them are neural neoplasms and are related to von Recklinghausen's disease. Pigment cells are a particular differentiation of nerve elements.

Nearly all extraocular malignant melanomas develop from nevi, and Albers[1] has recently suggested that intraocular melanomas, benign and malignant, also develop from nevi. A nevus in the region of the eye is like a nevus or mole anywhere else on the body. A pigmented mole consists of an accumulation of pigment and a mass of nevus cells in the corium. These cells are in intimate contact with the nerves of the skin. Masson[13] has shown that this pattern of nevus cells and nerves is a reproduction of the innervated tactile spots of reptiles. It is a transition from reptilian to mammalian sensory organs, and in the human being represents a reversion to type. When a pigmented mole becomes malignant, it develops into a neural tumor or a melanoma, but not a true sarcoma.

In 1937, Georgiana Theobald[22] made serial sections of seven so-called choroidal sarcomas, showing clearly that these tumors originate from the Schwann sheath cells of the ciliary nerves as they pass through the choroid.

All evidence today points, without much doubt, to the fact that these highly malignant intraocular and extraocular tumors, either lightly or deeply pigmented, hitherto called melanosarcomas, are actually ectodermal tumors of nerves and possibly all originate from nevi. Masson's[13] conception of the origin of the pigmented mole and of the malignant tumors which develop from it is today the one most widely accepted. The literature on this subject is filled with discussions and evidence supporting the epithelial versus the connective tissue origin of nevi.

Details regarding intraocular melanoma will not be reported here because its usual symptoms and manifestations

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

are generally thoroughly known. Its confusing and misleading characteristics have been completely described recently by Terry.[21] However, some mention should be made in this regard.

Samuels[19] has emphasized how often tumors of the iris are diagnosed incorrectly. He urges that when such a lesion is suspected, serology is indicated, and x-ray examination should be done in an attempt to find an imbedded foreign body. The degree of malignancy cannot be determined by the age of the patient, for a malignant melanoma of the iris has been proven to be present in a patient six months old. Iridectomy alone is often an insufficient procedure for eradication of malignancy of the iris; enucleation of the eye is the procedure of choice.

In cases of choroidal melanoma where enucleation has been carried out, the microscopic examinations revealed that 36 per cent of the patients had extension of the disease. This percentage of patients died as a result of metastases — about two-thirds within five years and about one-third five to ten years afterwards. Many authors agree that results should be evaluated over a ten year period rather than a five year period. The prognosis in cases of intraocular malignant melanoma is so unfavorable that von Hippel[11] maintained enucleation is relatively useless except in cases where the disease is present in its early stage. Early recognition of the tumor is of primary importance.

Terry[21] reports that malignant melanoma was not diagnosed clinically in 44 per cent of a series of cases in which enucleation was carried out. Because 30 to 40 per cent of the patients with such tumors eventually die as a result of metastases, he stresses that failure to recognize the presence of the tumor and enucleate the eye are greater mistakes than to enucleate an eye in which an erroneous diagnosis of neoplasm has been made. His extensive investigations revealed many errors which are made frequently in the treatment of such tumors.

Pigmented lesions which develop externally to the eye occur more frequently than those which form within the eye. Congenital pigmentation flecks on the bulbar conjunctiva are not uncommon. Rarely do they become malignant, but are considered to be potentially malignant. As a rule, a pigmented lesion in the bulbar conjunctiva undergoes little change during a lifetime. However, Reese,[17] in 1938, reported several rare cases of this type in which a diffuse malignant melanoma developed during later life.

Pigmented lesions external to the eye are similar to the ordinary pigmented moles or congenital nevi which form on other parts of the body. The majority of extraocular malignant melanomas develop on nevi. A careful study of an unusual series of cases of conjunctival nevi seen at the University Hospital at Ann Arbor has led to the following conclusions:

1. A conjunctival nevus is a rather common tumor which is sometimes overlooked.
2. It may appear clinically to be carcinoma.
3. It may appear on microscopic section to be carcinoma.
4. It is often difficult to determine what type of treatment is indicated because the lesion may be or may become highly malignant. However, ordinarily it is benign.

A cutaneous nevus or mole or benign melanoma is supposedly an epidermal fetal rest, manifest at birth, or dormant and appearing during adolescence or later. It remains unchanged except for growth as the body grows. Clinically, it may vary from a small, flat, pigmented macule to a large, verrucous, giant

nevus. Histologically, as seen in skin and conjunctiva, a nevus is composed essentially of groups of cells, which are round or cuboidal, occurring singly or in groups, with large, deeply staining nuclei and a moderate amount of pink-staining cytoplasm. The treatment of the pigmented mole of the skin is not well standardized,[2] there being disagreement over which methods of eradication are safe and which are dangerous. Malignant change is infrequent, and the routine removal of all nevi as prophylaxis is not practical. It is agreed that a nevus subject to irritation should be removed as well as a pigmented lesion showing possible malignant change such as recent development, growth, inflammation, or change in color. The amount of pigmentation is, however, no accurate indication of the degree of malignancy or rate of growth. For the treatment of moles in the skin, simple excision, dessication, and irradiation are used. There is disagreement, however, with regard to the relative reliability of each. The value of radiation therapy on pigmented lesions is disputed even among radiologists. Application of these methods to ocular lesions usually requires modification to avoid damage to vision.

FIG. 1 — Two conjunctival nevi on left eye of boy of 11 years. Present one year and growing. Excised 1918. No. pigment. No recurrence in 22 years.

Conjunctival nevi are ocular manifestations and are identical to pigmented moles on other parts of the body. They occur less frequently, but have the same structure, growth characteristics, and potential ability to invade. Characteristically, a conjunctival nevus (Fig. 1) is a slightly raised tumor located adjacent to the cornea, usually in the palpebral fissure. It is flesh colored, pink, or yellowish brown, the shade depending on the amount of melanin present. It is firmly attached and fixed at the limbus, but freely movable with the conjunctiva in which it rests beyond the limbus. Frequently one or more large conjunctival vessels enter it from the nearest canthus. Its surface appears to be smooth, not ulcerated; but close inspection reveals it to be granular, or finely lobulated. It may encroach slightly on the cornea. Pigment may or may not be present. Superficial examination may reveal it to be brown, while examination with the slit lamp may reveal fine golden brown pigment granules. On the other hand, pigment may be entirely absent. Examination with the slit lamp always shows a rich capillary blood supply. It also reveals, almost uniformly, a collection of small, round, clear spaces like tiny bubbles within the substance of the tumor. These vacuoles may vary in number, but they have been found so frequently by slit lamp examination that their presence is considered to be of diagnostic importance.

These tumors are semi-transparent, often are triangular or crescent-shaped, and lie near the cornea. They are congenital, or appear before or during adolescence. Their growth often is slow, and occasionally they seem to originate as a result of trauma. They may cause no symptoms, and the patient may be unaware of their existence. On the other hand, there may be mildly irritative symptoms supposedly due to pressure by the lids. The vision is never affected unless the tumor is malignant. Although they usually lie near the limbus and in the palpebral fissure, they also may appear elsewhere on the bulbar conjunctiva (Fig. 2) or in the caruncle or semilunar

fold. Often the only reason why a patient may desire to have the tumor removed is for the cosmetic effect.

FIG. 2 — Conjunctival nevus, right eye, male of 39 years. Present since childhood. Slowly growing. Size 10x7x1 mm. Histologically benign. Many large vacuoles. No pigment. Excised 1934. No recurrence six years.

Histologically, the conjunctival nevus has two fundamental characteristics, each varying in degree. The first is the presence of nevus cells, as already described. The other is that the surface epithelium almost invariably contains numerous club-like extensions or pegs into the subepithelial tissues, and there may be islands of epithelium in these deeper zones (Fig. 3). These pegs and islands of epithelial cells are intermingled intimately with the clumps and masses of nevus cells. This unusual extension downward of surface epithelium has often been the cause for the tumor being called a carcinoma or nevocarcinoma. In these epithelial islands and extensions, spaces very frequently form which are lined by epithelium. (Fig. 4 and 5.) They seem to be true cysts, although an origin in cellular degeneration has been suggested because of the presence of goblet cells. These spaces vary in number and size and can be seen with the slit lamp. When pigment is present, it consists of golden brown particles of melanin anywhere in the tumor mass. (Fig. 6.)

Many of the conjunctival tumors described in the past under a variety of names were probably nevi. These variations in nomenclature have been confusing as far as etiology, diagnosis, and treatment of nevi are concerned. Because of the cystic spaces, the names NEVUS PIGMENTOSUS CYSTICUS, TELANGIECTATIC ADENOMA, and BENIGN CYSTIC EPITHELIOMA were given. PARINAUD'S DERMOEPITHELIOMA and FEHR'S GELATINOUS TUMOR were names which probably represented nonpigmented nevi. These tumors have been classified as various types of carcinoma, and, when pigmented, have been called both melanotic epitheliomas and sarcomas. Since the work of Masson reveals the nevus to be

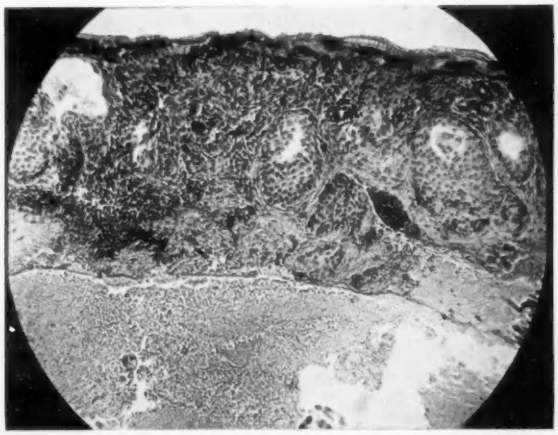


FIG. 3 — Photomicrograph of conjunctival nevus showing numerous epithelial pegs and islands among clumps of darker nevus cells.

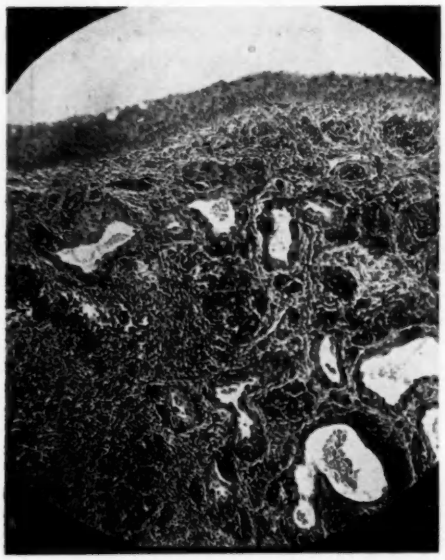


FIG. 4 — Photomicrograph of conjunctival nevus showing spaces formed in subepithelial islands of epithelial cells. Clumps of nevus cells are intermingled.

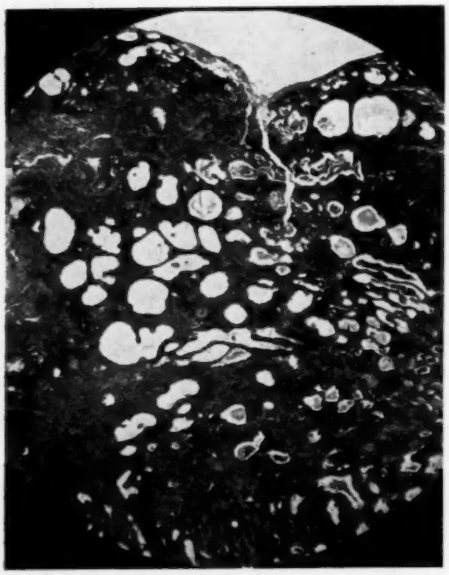


FIG. 5 — Photomicrograph, low power, of conjunctival nevus, showing innumerable cystic spaces or vacuoles in a solid nevus tissue. These spaces can be seen in vivo with the slit lamp.

FIG. 6 — Photomicrograph of conjunctival nevus showing clumps of melanin pigment scattered through the lesion.

of neural origin, whether pigmented or not, the nomenclature can be clarified by placing these tumors into two categories as Duke-Elder[6] does in his second volume, namely:

1. *Nevus* to connote the usual benign tumor.
2. *Malignant melanoma* to connote the malignant development therefrom.

Malignancy in such tumors is often difficult to determine and prove. Upon the answer to that problem depends the choice of method of treatment, and upon the success or failure of the treatment rests the loss of an eye or even the loss of a life. Should a conjunctival nevus become malignant, it would show characteristics of any pigmented or potentially pigmented tumor. The presence and degree of malignancy often can be determined only by microscopic examination of the tissue, and this does not always distinguish the fine demarcation which sometimes exists between malignant and non-malignant neoplasms.

Removal of these tumors is advocated in the literature. As an example, Fuchs[9] said that since benign moles sometimes develop into malignant tumors, one is justified in removing them early. The

consensus of opinion[4,23] seems to be that the degree of malignancy cannot accurately be determined clinically, but for the sake of precaution these lesions should usually be excised rather radically.

As an example of what can occur we refer to a case reported by Smith.[20] The patient was a man 39 years old in whose conjunctiva a brown spot had been present since birth. The growth had shown signs of progress for seven years. On two occasions excision was carried out, and finally irradiation was resorted to. The patient died as a result of metastasis from a malignant melanoma. Fuchs[10] in his Atlas reports the case of a woman 56 years old in whom a malignant change in a congenital melanoma was present. The neoplasm had begun to grow two years prior. Ewing[8] reports a fatal case. Rodin and Hall,[18] in reporting malignant melanoma in a boy of six years, discovered 12 similar cases had been reported in the literature over a period of two years. McKee,[12] Pohissov,[16] Neeper,[15] Castroviejo,[5] Zeitler,[25] Ball and Lamb,[3] and Merrill[14] have reported cases of malignant change, often fatal, occurring on congenital nevi.

I shall review the cases of 12 patients in whom a total of 13 conjunctival nevi were diagnosed at the University Hospital in Ann Arbor. Their ages ranged from 7 to 39 years and averaged 16 years. Seven were males, and five were females. The known duration of the tumors varied, in some cases it was six months and in others it was a lifetime. Most of the patients sought medical advice concerning spots on the conjunctivae which were symptomless. Growth of the tumors had been noticed in eight cases, and in one case there had been no increase in size. In three cases the patients could not state definitely whether the tumors had been growing or not.

The lesions were removed by excision. Scissors were used to free the lateral side of the tumor from the loose conjunctiva, and the knife was used to free the growth from its firm attachment at the limbus. The defect over the sclera was covered by drawing the adjacent conjunctiva over it. Actual cautery was used on the denuded area in nine cases. Irradiation was administered postoperatively in four cases, and in one case radium was used. Irradiation was not given in the remaining cases. Convalescence was uneventful in all cases but two, in which there were moderately severe local reactions which eventually subsided. A frozen section was made of five of the tumors during operation, and basal cell carcinoma was diagnosed in all of them. One of these diagnoses was later changed to nevus. Microscopic examination of the tissue removed in the 13 cases revealed four of the tumors to be squamous cell carcinomas, two basal cell carcinomas, and seven nevi. One of the latter was classified histologically as carcinoma. Excision was inadequate according to the microscopic examination in six cases and questionably inadequate in three cases.

Examination with the slit lamp prior to surgery revealed pigment granules in only two of the tumors and no pigment in the others. In one of the tumors which contained pigment, this was present only near the limbus and the tumor might have been considered non-pathologic. The pigment in the other lesion was seen also on section. Examination with the slit lamp revealed vacuoles in all but two of the tumors. One error each way was made in this regard in confirming slit lamp findings with microscopic findings. The visual acuity was not affected in any case. In nine cases the color of the lesion was pink, shading off to yellow or brown, and in one it was yellowish pink. In cases where the tumor was present in the left eye, it was temporally or temporally obliquely from the cornea. When it was present in the right eye, it

was either temporally or nasally to the cornea. Size of the growths varied from 2x1½ mm. to 8x12 mm. Fifty per cent of the lesions extended somewhat onto the corneae, the greatest distance being 3 mm. (Fig. 7.) The shapes varied; some were oval, some quadrilateral, some crescent or comma shaped, and some triangular. Epithelial spaces or cysts beneath the surface were seen in

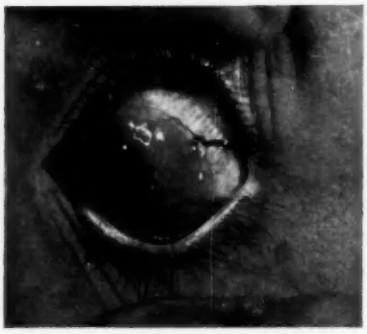


FIG. 7 — Conjunctival nevus, left eye of a girl of 8 years. Present 4 years, growing. Size 8x12 mm. and onto cornea 3 mm. Largest in this series, surrounding half of cornea. Unusually large and numerous vacuoles. Very solid nevus tissue. No pigment. In section was highly suspicious of malignancy. Excised 1934. No recurrence six years.

over 80 per cent of the sections, and most of these had been seen preoperatively during examination with the slit lamp. The number of spaces and their sizes tallied closely when comparing the microscopic examination with that with the slit lamp.

The first patient in this series was only 11 years old when two lesions were removed from his left eye at the University Hospital in 1918. The first lesion was diagnosed squamous cell carcinoma and the second basal cell carcinoma. Cautery or irradiation were not used. The patient is living and well and reports that he has had no further trouble nor recurrence. The next eight patients were treated in 1934 and 1935. I have heard from each of them during the last few months. There has been no further trouble nor recurrence in any of these cases. The remaining cases were treated so recently that a followup at this time would be of little value.

I have all the data, including tissue section, on another patient whom I saw but who was operated upon elsewhere. Also, a diagnosis of nevus was made in the case of a boy eight years old, and

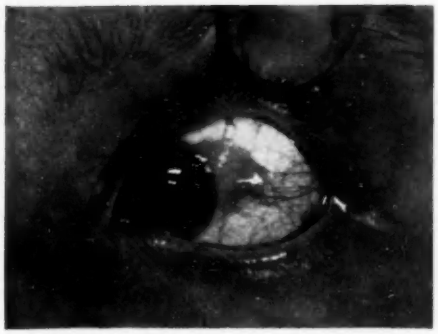


FIG. 8 — Conjunctival nevus, left eye of a girl of 14 years. Present 12 years. Growing. Size 7x12 mm. Unusually solid nevus with many vacuoles. No pigment. In section showed inadequate excision. Removed 1934. No recurrence in six years.

surgery was advised but was refused. At the present time a girl 16 years old is under my observation for a large typical nevus on the conjunctiva of one eye and a smaller but similar lesion on the other. If these last four cases are included in this series, the total number is 17. All of the tumors in the cases reported were at or near the limbus. (Fig. 8.)

Pigmented lesions of the conjunctiva elsewhere, such as on the lids, the semilunar fold, or the caruncle (Fig. 9), present about the same characteristics as those on the bulbar conjunctiva and fundamentally the tumors are the same. However, malignancy occurs in the former much more frequently. Adequate excision of a tumor of the lids, semilunar fold, or caruncle is not difficult, and the procedure is not accompanied by

risk of injuring the globe or disturbing vision.

Pigmented lesions of the caruncle are relatively rare, but are often fatal. Wetzel,[24] in 1937, found only 29 cases reported in the literature, and he added one of his own. The lesions occurred in patients of all ages. Occasionally trauma, and often puberty, seemed to precede the development of malignant changes. In

FIG. 9.—Malignant melanoma of right caruncle in a girl of 16 years.

three cases there was a history of a nevus since childhood, and in three other cases evidence of nevus was found on tissue section. Definite recurrence after excision occurred in ten cases. Evans,[7] in a recent study of 200 cases of lesions of the caruncle, listed 74 in the nevus group and found them to show more of a degree of benignness than is found generally in melanomas.

Pigmented extraocular lesions in younger people are usually benign. However, close observation from time to time is necessary because definite evidence of malignant changes sometimes occurs. In older people these lesions more frequently are found to be malignant.

In treating cases of pigmented extraocular lesions, complete removal of the lesion is necessary. If this is not accomplished, the patient would be better off without any treatment at all. I am not sure that our treatment of the cases reported in this series has been radical enough. Although some physicians recommend irradiation in large doses, our local consultants feel that such radiation has little or no effect on pigmented or non-pigmented tumors. Cauterization is probably the best way of treating tumors on the eyeball when enucleation of the eye is indicated but is not undertaken or is not permitted.

In this presentation a brief review of the literature has been attempted, reiteration of the difficulties in diagnosing and treating pigmented, non-pigmented, malignant, and benign intraocular and extraocular lesions has been undertaken, and the potential fatalities of such lesions have been considered.

I wish to thank Doctors F. B. Fralick, C. V. Weller, R. C. Wanstrom, F. H. Verhoeff, and G. M. D. Theobald for their help in making this study.

REFERENCES

1. Albers, E. C.: Benign Melanomas of the Choroid and Their Malignant Transformation, Am. J. Ophth. 23:779 (July) 1940.
2. Anderson, H. F., and Simpson, C. A.: Pigmented Moles and Their Treatment, Am. J. Roentgenol. 33:54 (Jan.) 1935.
3. Ball, J. M., and Lamb, H. D.: Epibulbar Melanotic Tumor of the Limbus, Soc. Tr. Arch. Ophth. 52:80, 1923.
4. Benedict, W. L.: Clinical Considerations of Melanotic Neoplasms of the Eye and Orbit, Surg., Gynec., and Obstet. 64:513 no. 2A (Feb.) 1937.
5. Castroviejo, R., Jr.: Epibulbar Nevocarcinoma with Almost Total Corneal Involvement, Am. J. Ophth. 14:757 (Aug.) 1931.
6. Duke-Elder, W. Stewart: Text-book of Ophthalmology, St. Louis, C. V. Mosby Co., 1938, vol. 2, p. 1805.
7. Evans, W. H.: Tumor of the Lacrimal Caruncle; Study of 200 Collected Cases, Arch. Ophth. 24:83 (July) 1940.
8. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, Saunders, 1928, p. 931.
9. Fuchs, Ernest: Diseases of the Eye, 10th English ed., Philadelphia, J. B. Lippincott, 1933, p. 124.
10. Fuchs, Adelbert: Atlas of Histopathology of the Eye, Leipzig and Vienna, F. Deuticke, 1927, part 2, plate 8, 1 and 2.
11. von Hippel, E.: Fortsetzung meiner Sarkom-Statistic, Arch. f. Ophth. 129:552 (Mar.) 1933 and Arch. f. Ophth. 135:76 (Jan.) 1936.

12. McKee, J. W.: Melanosarcoma at the Limbus, Am. J. Ophth. 13:407 (May) 1930.
13. Masson, P.: Les Naevi Pigmentaires, Tumeurs Nerveuses. Ann. d'Anat. Path. Med-Chir., Paris, 3:417 (May) 1926 and 3:657 (July) 1926.
14. Merrill, Rowland H.: Malignant Melanotic Tumor of the Limbus, Soc. Tr. Arch. Ophth. 17:747 (April) 1937.
15. Neeper, E. R.: Melanosarcoma of Bulbar Conjunctiva, Soc. Proc. Am. J. Ophth. 11:135 (Feb.) 1928.
16. Pohissov, N. I.: Histogenesis of Pigmented Nevi of the Conjunctiva, Russki Opht. Jour. p. 779 (June) 1930.
17. Reese, A. B.: Precancerous Melanosis and Diffuse Malignant Melanoma of Conjunctiva, Arch. Ophth. 19:354 (Mar.) 1938.
18. Rodin, F. H., and Hall, E. M.: Nevus of Bulbar Conjunctiva; Report of Case, Am. J. Ophth. 12:24 (Jan.) 1929.
19. Samuels, B.: Intraocular Tumors, Pennsylvania M. J. 36:895 (Sept.) 1933.
20. Smith, James W.: Melanoma of the Conjunctiva — Fatal Termination, Soc. Tr. Arch. Ophth. 12:623 (Oct.) 1934.
21. Terry, T. L.: Malignant Melanoma — So-called Sarcoma — of Uvea; Problems in Diagnosis, Arch. Ophth. 22:989 (Dec.) 1939.
22. Theobald, G. D.: Neurogenic Origin of Choroidal Sarcoma, Arch. Ophth. 18:971 (Dec.) 1937.
23. Torgersruud, T.: Quelques Cas de Naevus de la Conjonctive, Acta Ophth. 13:77, 1935.
24. Wetzel, J. O.: Melanoblastoma of the Lacrimal Caruncle; Report of Case and Review of Literature, Am. J. Ophth. 20: 675 (July) 1937.
25. von Zeitler, Dr. Maria: Zur Klinik der Epibulbaren Tumoren, Ztschr. f. Augenh. 82:3, 1933.

DISCUSSION

GEORGIANA D. THEOBALD, M.D., Chicago: During the past two years I have examined 34 specimens of nevi which occurred about the eye. Thirteen were found on the bulbar conjunctiva, four of which were at the limbus. One was found on the left caruncle and the other 20 occurred in various regions of both upper and lower lids. Of the latter group, two were recurrences and showed no malignant tendencies. The ages of the patients ranged from five weeks to 77 years, and the average age was 35 years. Fifteen were males, and 19 were females. Two cases were from my own practice, and 32 cases were treated by surgeons at the Illinois Eye and Ear Infirmary.

In the cases in which the nevus was present on the caruncle, pigmentation was observed by the mother when the girl was three years old. I removed the growth when the patient was five. The caruncle was excised as deeply as possible. The excised specimen showed nevus cells at the cut edge. Because it was impossible to know how deep into the tissue the nevus extended, radium treatments were given. Although the result seems to be perfect, the case will be observed for recurrence of the growth.

Although malignant degeneration of nevi is not frequent, it is justly feared; for when it does occur, metastases quickly develop and the result is fatal.

A man in his twenties consulted at the Illinois Eye and Ear Infirmary because of a rapidly growing mass at the limbus of one eye where a pigmented nevus had been present as long as he could remember. Two months previously he had been struck across the eye by a branch from a tree. The eye was enucleated, but already there were metastases to the glands of the neck. This tumor consisted of large epithelial cells, and pigment cells were interspersed among them.

I wish to emphasize the necessity of complete removal of the tumor at the time of excision. First, because of recurrence if all the nevus cells are not completely removed, and second, because nevi tend to become malignant after irritation. When removing such a tumor, it must be excised widely.

Doctor Marshall has covered the subject well. I am glad to add these cases.

BERNARD SAMUELS, M.D., New York: Doctor Marshall has admirably accomplished what he set out to do, namely, to review briefly malignant melanomas of the globe and adnexa and to report his own clinical and pathological observations in a series of thirteen nevi in the epibulbar conjunctivae of twelve globes. So far as local recurrence is concerned, the excision of nevi of the conjunctivae is as a rule successful, otherwise mention of enucleation of the globe or exenteration of the orbit, owing to the spread of the tumor, would be more frequently found in the reports of the large eye hospitals. Every year at the New York Eye and Ear Infirmary a number of nevi of the conjunctivae and eyelids are excised and examined under the microscope, but only once in the past three or four years has an exenteration

of the orbit been necessary because of intractable local recurrence. This patient died of metastasis within a year.

Death as a result of malignant melanoma of the eye and the skin is, after all, rare. Agatston and Gartner, in 1939, as a result of a survey of its incidence, ascertained that out of one million of the white population in this country less than two died each year as a result of malignant melanoma.

I agree with Doctor Marshall that if one attempts to excise a nevus he should, so to speak, go at it with shovel and tongs. Especially, he should excise well beyond the nevus along the ill-defined margins facing the retrotarsal folds. This zone is more dangerous for recurrence than that facing the corneal zone. The cornea and sclera at the limbus offer stubborn resistance to proliferation of nevus cells. Ordinarily one can excise the tumor cells at the limbus by dissecting deeply into the tissues as in a trephine operation. However, along the opposite border the tissues are loose, and here tumor nodules may spread rapidly far and wide over the globe and may be difficult to distinguish clinically unless heavily pigmented. In the end, they may penetrate the tarso-orbital fascia. Once beyond this barrier, it is certain that no form of irradiation can destroy them.

In my opinion, the use of the actual cautery over the area denuded by the excision of a nevus or malignant melanoma is of little avail. The bulk of a conjunctival nevus or early malignant melanoma is readily lifted away from the underlying sclera which can be accurately cleaned by dissection. If the tumor cells have penetrated deeply at the limbus or have spread into the loose tissues at the retrotarsal fold, it is not likely that they will be reached with the cautery. In my limited experience, irradiation to malignant melanomas of the conjunctiva and eyelids has only succeeded in delaying the progress of the disease, which no sooner is brought under control in one area than it breaks out in another.

Usually an epibulbar nevus is supplied by one or two large blood vessels exposed superficially in the conjunctiva. In examining a nevus for the first time, or in keeping one under observation, it is my habit to pay particular attenion to its visible blood supply. If a vessel enlarges and becomes engorged, my impression is that the nevus cells are proliferating and entering into the realm of malignant melanoma, no matter whether there is increase in pigmentation or not. Although malignant melanoma derives its name from melanin, yet melanin is not an essential element to it or to a nevus.

As Doctor Marshall has pointed out, what for years were described as sarcomas of the uveal tract are now considered to be of ectodermal origin and to be derived from the Schwann layer of syncitial cells surrounding a nerve. Nevi of the conjunctiva and of the skin are believed to have a similar origin. In von Recklinghausen's disease the fibromas also rise from neuroectoderm. Therefore, there is an intimate relationship among all malignant melanomas whatever their location, whether in the uvea, the conjunctiva, or the skin. Moreover, malignant melanoma of the choroid and multiple fibromatosis of von Recklinghausen's disease have been reported a few times to have been present in the same person, and the occurrence was not considered to be a mere accident. This leads to the question of whether gelatinous nodules with or without pigment (moles) were observed in the skin in association with the nevi of the conjunctivae which Doctor Marshall reports.

Recently, I enucleated an eye because of a malignant melanoma of the iris. In this case it was interesting to note that a number of moles, some of which were pigmented, were present on the skin of the face and neck. I excised one large mole that was in the skin of the eyebrow on the same side as the intraocular tumor, and I found that it was composed of typical nevus cells. In this case, by superficial examination, one beheld malignancy on the inside of the globe and potential malignancy in the adnexa.

MYCOTIC INFECTIONS OF THE RESPIRATORY TRACT

WILLIAM D. GILL, M.D.
SAN ANTONIO, TEXAS

THE MYCOSES probably constitute the most widespread type of infection from which mankind suffers, rivaling the common cold in their universal tendency to attack the human subject. There are few persons who have not suffered from one or more of the milder forms of mycotic infection such as ringworm or the so-called athlete's foot, a form of mycosis which is almost common-place. Many lower animals are affected by certain types of mycoses, and one has but to mention a few of them, such as actinomycosis or lumpy jaw of cattle, torulous infection of the lungs of horses, and cattle ringworm to emphasize the fact. Mycotic fungi or molds are widely distributed in nature, and their spores are almost always present in the air. Fortunately, most of these are non-pathogenic. The disintegrating process in organic matter is often accomplished through the action of molds, and both pathogenic and non-pathogenic forms are easily isolated from a variety of sources, such as decaying vegetation, leaves of various plants, and a multiplicity of prosaic objects too numerous to mention. Many of the molds are, under ordinary conditions, harmless to the human host, but some of the supposedly innocuous species are facultatively pathogenic under suitable conditions.

The action of the higher fungi is an important influence in some industries, as illustrated by the fact that in the manufacture of certain kinds of cheese, such as Roquefort, the flavor is dependent upon the action of the fungus Penicillium Roqueforti, and soy bean sauce is made by the action of a type of Aspergillus.

Considerable confusion surrounds the nomenclature and classification of pathogenic fungi, but there are a few ardent investigators who are diligently working to overcome this handicap. The work of Castellani[8] has been outstanding in this respect.

It is most convenient, for the purpose of study, to divide the molds into (1) yeastlike or budding fungi; (2) filamentous fungi; and (3) higher bacterial forms.

I. Budding fungi
   1. Saccharomycetes
   2. Moniliae
   3. Torulae
   4. Oidiae
   5. Blastomycetes
   6. Coccidioides
   7. Sporothrix

II. Filamentous fungi
   8. Aspergilli
   9. Penicillia
   10. Mucors

III. Higher bacterial forms
   11. Actinomyces
   12. Nocardia — or — Streptothrix
       acid fast
       non acid fast

The above list is by no means complete, but it will serve as a satisfactory guide for the clinical classification of the pathogenic molds ordinarily encountered. One could amplify this list considerably by adding the molds whose spores produce allergic reactions.

The pathogenic molds, which are the chief offenders in producing lesions in

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

the respiratory tract of the human host, are the Aspergilli, the Oidiae, the Penicillia, the Moniliae, the Mucors, the Coccidioides, the Actinomyces, and at times the Saccharomyces, as well as several other less well known varieties. Infection with budding forms is often designated as blastomycosis with no mention of the exact type of organism causing the local lesion. Exact classification of a lesion described under this term is impossible due to the fact that there are many pathogenic budding forms. Medical writers should designate the responsible organism if they have been able to culture and classify it, and in the absence of this information the fact should be stated.

In pathological conditions of the respiratory tract, molds are often found in association with other organisms, particularly in bronchiectasis or in the presence of neoplasms. Gunter[30] has reported an interesting case of mixed spirochetal and fungous infection of the lungs. Molds are often encountered as contaminants in the mouth or in the sputum, and they may be either pathogenic or non-pathogenic types. It is an easy matter to dispose of molds from the etiological standpoint by regarding them as contaminants, but this is an inexcusable subterfuge to use in order to escape a more thorough investigation to establish their real significance as possible producers of disease.

Susceptibility to fungous infections varies with individuals, some persons being extremely vulnerable to their attacks, others showing an unquestionable degree of immunity. Deficiency in certain vitamins may increase susceptibility to invasion with pathogenic fungi through alteration of surface epithelium. In general, it may be said that any condition lowering the hydrogen ion concentration of the secretions, making them more acid, favors fungous growth. Individuals with abnormally high blood sugar values apparently are more susceptible to mycotic infections. Macfarlan[41] believes that any condition producing abnormal drying of the mucosa predisposes to fungous infection. Geographically, the pathogenic fungi are ubiquitous. They produce disease with greater ease in tropical and subtropical countries where conditions of temperature and moisture are most favorable for their growth, but even the colder climates are not a certain protection against them. Clinical reports from widely separated areas emphasize this fact.[60,24,29]

SYMPTOMATOLOGY

During the time allotted, it would be impossible to discuss exhaustively all the symptoms which are present in fungous infections of the respiratory tract, and only the most important symptoms will be considered.

The objective findings vary somewhat with the type of organism causing the local lesion, but generally speaking there are no specific diagnostic features characteristic of all mycotic infections in their early stages. The clinical diagnosis always must be confirmed by adequate laboratory investigation. The resistance of the lesions to the usual local measures of treatment and their tendency to become chronic is strong presumptive evidence of mycotic infection.

The milder forms of involvement of the mucous membrane with the Monilia present whitish, opalescent, filmlike exudation as their chief characteristic. In the lungs Monilia produces a chronic pneumonitis associated with marked physical impairment, which runs a clinical course simulating tuberculosis, as pointed out by Castellani,[9,10] Stovall,[58] and others.[48,51,3,19,36,52] Such infections are often fatal and they may be very acute and fulminating in character.[15] Acute pulmonary infection with Monilia may be confused with pneumonia.[32,33]

In torulous infection the chief characteristic of involvement of the mucous membrane is ulceration. The lesions begin as nodules which soon soften and slough, producing ulcers with elevated, hard, infiltrated edges so that in advanced stages an excavated, or scooped-out, appearance is noted in the areas affected.[27] The tendency for the lesions to coalesce is quite marked. The fauces, tonsils, and the pharyngeal mucous membranes are the sites of predilection for Torulae. Filamentous lesions of the dorsum of the tongue due to Torulae have been reported.[1,28] The lesions caused by this fungus are indolent in character and have a marked tendency to invade the blood stream and give rise to a highly fatal type of meningo-encephalitis. A search of the literature fails to reveal a single instance of invasion of the central nervous system with Torulae in which recovery has taken place; and almost without exception, in the reported cases, the atrium of infection has been a lesion in the upper respiratory tract which may have been controllable in its incipiency by simple measures.

The sulphur granules formed in actinomycotic infections are considered characteristic of this type of infection. They occur in the exudate thrown off from the lesion. Superficial actinomycotic infections show an encouraging percentage of recoveries, but involvement of the lungs is invariably fatal.

The Coccidioides produce a granulomatous type of lesion of the mucocutaneous junctures about the nostrils and mouth which is manifested by a relatively mild course; but when visceral involvement takes place, it is usually in the form of a pulmonary involvement which has a startlingly high mortality, although it is by no means hopeless, as instances have been recorded of arrested pulmonary involvement.[13] The greater number of cases of this disease that have been reported have originated in California, but it is by no means limited to that state as it is sometimes thought to be.

The Oidiae produce lesions of the mucous membrane appearing as milky white patches to which the older writers refer as thrush.

The Streptothrix invades the tonsil with the production of warty, tough excrescences which are difficult to eradicate but which are relatively harmless to the host. Resulting pulmonary invasion with the production of pseudotuberculous pneumonitis has been reported.[37]

The Aspergilli may grow on the surface of mucous membranes using the living tissue as their substrate and producing areas in which the conidia or spore capsules appear as coal black granular particles. Such lesions may cause marked local symptoms, and for this reason if for no other, they hardly can be regarded as mere Saprophytes. The writer has seen one patient with pulmonary aspergillosis who at intervals coughed up quantities of spores resembling finely powdered charcoal and another instance in which there was massive involvement of the tonsil and dorsum of the tongue with the Aspergillus niger. In several instances the nasal accessory sinuses have been reported to be involved by the Aspergillus. Foster[25] and Stevenson[57] have encountered such infections in their practices.

Instances of laryngeal mycosis have been reported by Jackson,[34] New,[44] Clerf and Bucher,[11] Downing,[18] and Dennis.[17] Granulomatous masses, which are somewhat like the surface of a blackberry in appearance, occur in the larynx in this condition.

The diagnosis of mycotic infection in the deeper tissues of the respiratory tract is not always easy. Invasion of the lungs by pathogenic fungi produces a chronic, progressive type of pulmonary

inflammation which quite often is mistaken for tuberculosis. Pulmonary involvement produced by one of the pathogenic fungi should be suspected in any patient who is running a clinical course suggestive of tuberculosis where there is a consistent absence of tubercle bacilli in the sputum and where the x-ray findings do not conform to the well-known picture of tuberculosis, particularly when such findings occur in association with sputum that is blood-tinged.[16] As pointed out by Stovall and Greely[58] and also by Penta,[46] there are no physical signs which are specifically diagnostic of fungous infection of the lung tissue, but the consensus of opinion is that in fungous disease of the lungs there is usually strikingly evident disproportion between the amount of pathology present and the symptoms. In most mycotic infections of the lungs, the patient is not as ill as the pathology would indicate. Notable exceptions to this statement occur in pulmonary actinomycosis, coccidiosis, and torulosis.

Skin testing with filtrates made from the various fungi often assists in pointing the way to the responsible organism and makes differential diagnosis more certain. Smith and Lewis[55] have recommended the use of an autogenous filtrate for this purpose. At the present time commercially prepared filtrates for many pathogenic fungi are available. In the presence of mixed infections, the problem of differential diagnosis becomes more difficult, as both tuberculosis and pulmonary mycosis may exist coincidentally. In the final analysis, the diagnosis of mycosis of the respiratory tract rests on repeatedly finding the fungus in the exudate from a lesion or in the discharges thrown off by way of a sinus tract or through the natural passages such as the trachea. The isolation of fungi requires a specialized laboratory technic and the use of selective culture media. One important factor which often is overlooked and which is responsible for many missed diagnoses is the failure to retain cultures long enough to permit the fungi to attain full growth. A culture made for diagnostic purposes should not be discarded before it is two weeks old. Martin and David Smith[42,53] recommend retaining cultures as long as four weeks before discarding them, and they state that even with grossly contaminated plates it is quite often possible to isolate the colonies of pathogenic fungi.

The use of the agar slant method, as well as ordinary plating in Petri dishes, is the commonly practiced method of making cultures for pathogenic molds. However, for the purpose of studying the physical characteristics of the cultures, the slide method, whereby the organism is implanted in a nutrient medium between two glass slides, is the preferable one, as in this way growth takes place on a flat sheet and lends itself more easily to direct observation and study. Cultures are usually obtained from secretions and exudates, but if possible it is equally important to obtain them by curettement from the depths of the lesion, as actual invasion of the tissues is demonstrable in this manner and the question of saprophytic involvement is differentiated. Biopsy in certain instances can be carried out, and the fungi can be demonstrated in the tissue sections. When this is done it is advisable to seal the lymphatics and blood vessels with some coagulant such as phenol or trichloracetic acid after taking the specimen for biopsy in order to limit the possibility of extension of the infection. The method of tissue examination for fungi, described by Weidemann,[66] is particularly valuable in making a diagnosis in certain fungous infections.

In the upper respiratory tract, cultures can ordinarily be obtained with ease; but when deeper portions are involved, such as the larynx, trachea, or

the lungs, then the problem is more difficult. Emphasis has been placed on this point by several writers, such as Looper[39] and Vadala[63] who point out that every institution treating pulmonary diseases should have, as part of its set-up, a well equipped bronchoscopic department, for in the final analysis the diagnosis of pulmonary mycosis resolves itself into a bronchoscopic problem. In this recommendation the writer concurs emphatically, as it offers the only means of obtaining uncontaminated secretions for study.

A complement fixation reaction on the patient's blood serum has been devised by Martin[43] who has reported its diagnostic value in a number of cases of blastomycosis.

Diagnostic procedures of value in establishing the presence of mycotic infection in the tissues of the respiratory tract may be summarized as follows:

1. Direct examination of the lesion.
2. Microscopic examniation of exudate and curettings from the lesion.
3. Biopsy with histological study of the stained section.
4. Culture of exudate and curettings on one of the selective media.
5. Slide culture for morphological study.
6. Skin testing with extracts or filtrates from pathogenic molds when applicable.
7. Complement fixation reaction on patient's serum (blastomycosis).

PROGNOSIS

The prognosis of mycotic infections of the respiratory tract varies with the invading organism as well as with the resistance of the host to the invader. The tissue reactions vary from mild, indolent lesions, such as those produced by the Oidiae, to fulminating types of disease, of which the Coccidioidal lesions present the most striking example. The least dangerous of the fungi are the Saccharomyces, which are only facultatively pathogenic; next in order, the Oidiae; and next, the Moniliae. The Aspergilli, Penicillia, and Torulae (the latter as long as it is a producer of local disease), may be classified as moderately dangerous, but potentially the Torulae are extremely dangerous to life. Actinomycotic as well as coccidioidal involvement of the lungs usually terminates fatally, while the Torulae, in most instances of pulmonary involvement, metastasize to produce a low grade type of meningo-encephalitis from which recovery does not take place.

The importance of controlling mycotic infections in their incipiency and when the lesions are purely local is strongly emphasized by the terminal features of most infections coming in this category.

A great variety of drugs has been utilized in attempting to control mycotic infections. Therapy applied to superficial lesions of cutaneous and mucous surfaces and those of deeper involvement, such as the visceral types, is varied. Broadly speaking, the therapeutic measures at our disposal may be divided as follows: (1) Topical applications; (2) Internal medication with drugs; (3) The use of vaccines or filtrates; (4) Radiant energy such as x-ray and radium; (5) Surgical measures.

Topical applications, utilized in the treatment of mycotic infections, have been legion. A few that have been used most effectively are iodine, colloidal copper, thymol, cresol preparations, antimony and potassium tartrate, mercurial compounds, and silver nitrate. Of all these, iodine apparently heads the list in effectiveness. It has been used undiluted or in the form of one of the salts such as sodium iodide or potassium iodide. Swartz,[59] Penta,[47] and David Smith[54] have recommended inhalation of ethyl iodide in cases of pulmonary mycoses in

which the patient is unable to take iodine or iodides internally. Monilial lesions of the mucous membrane ordinarily disappear with one or two applications of a weak solution of iodine, such as Lugol's solution. Pulmonary moniliasis is more difficult to influence. Weak iodine solutions may be used for irrigation of cavities such as the maxilliary antrum or sinus tracts. The writer's experience has been, in the main, disappointing when other drugs have been used as topical applications in the treatment of lesions of the upper portion of the respiratory tract. Next to iodine in effectiveness as fungicides are thymol and certain cresols. Metacresol acetate, which works so well on most cutaneous mycoses, is almost without effect on mucous membrane lesions due to the difficulty in having it remain in contact with the lesion for any length of time. A more prolonged contact is obtainable by mixture of the drugs with tincture benzoin, used as topical applications; a film is formed by precipitation and will remain for an appreciable period of time in situ.

Taken internally, iodine is about the only drug that has an outstanding degree of effectiveness. Colloidal copper in the treatment of coccidioidal granulomatosis has been reported as successful by certain observers.[35] Thymol taken internally is considered of value by other writers.[40]

Autogenous filtrate from the responsible organism used hypodermically has been of service to Robinson and Grauer.[50] It has been our own experience that this is of distinct value and should always be included in the therapeutic armamentarium when practicable. The filtrate made from the Coccidioides is designated as Coccidioidin.

Radiant energy is of the greatest value in treating certain mycoses, those of the mucous surfaces and their mucocutaneous junctures responding most favorably. Of the various forms of radiant energy at our disposal, we have found x-ray to be the best means of treatment. Ultraviolet light does not possess enough sterilizing effect to merit serious consideration, although it undoubtedly is inhibitory or restraining in its action on certain molds. Radium has not been so encouraging in its effects in the cases which we have treated with it. In pulmonary mycosis the use of x-ray therapy may, at times, prove of value, but usually the course of the disease is not materially influenced by it. Dosage is best left to the roentgenologist, but it should not in any instance be carried to the point of producing marked fibrosis of the pulmonary tissue.

Surgical measures, which may become necessary in the treatment of mycotic infections of the respiratory tract, vary in magnitude and range from simple excision of a local lesion with cauterization of the denuded area to major procedures in which portions of the chest wall or lung tissue must be removed. The results obtainable with surgical measures may be stated to depend in general on four factors: (1) The degree of involvement present; (2) The area involved; (3) The virulence of the organism; and (4) The patient's resistance. The more extensive surgical procedures are almost invariably disappointing and too much should not be anticipated from them. Only well sequestrated lesions should be considered adaptable to major surgical measures.

In any type of operation, even when taking a biopsy, vascular and lymphatic channels are opened which may easily permit extension of the infection elsewhere, and for this reason the use of cautery after excision, or the use of an electrosurgical knife is preferred. In the resistant cases there is very little that can be done to influence the course of the disease, and measures which have produced spectacular results in one pa-

tient may be wholly without effect in another.

We have had no experience with sulphanilamide and its related compounds in treating the mycoses, but perhaps in the further development of this group of drugs one will be encountered which will have properties of great value in treating mycotic infections.

This presentation would be incomplete without some mention being made of the relationship between molds and certain allergic phenomena.

Pennington[45] recently has called attention to the numerous species of molds that may produce hypersensitive reactions such as hay fever and asthma. Van Leeuwen[64,65] first investigated this problem in 1924 and stated that as high as 50 per cent of asthmatics show mold hypersensitivity. Through the interest which he aroused there has been a number of articles published on the subject since that time.[67,12,49,4,56,14,62,6,61,3] Frankel[26] found 16 per cent of asthmatics sensitive to fungi. Hopkins, Benham, and Kasten[31] demonstrated conclusively, in 1930, the occurrence of specific sensitivity to the alternaria. In 1930, Bernton[5] and, in 1931, Flood[23] demonstrated instances of hypersensitivity to the Aspergillus fumigatus and mucor plumbeus. Feinberg,[20,21,22] Lamson and Rogers,[38] and Brown[6] have made surveys to determine the incidence of hypersensitiveness to molds. Estimates vary widely from 12 per cent to 50 per cent, depending on the class of patients tested. Asthmatic patients give the highest incidence of hypersensitiveness, while it is lowest in persons selected at random, as would be expected.

The Association of Allergists[2] for Mycological Investigation is conducting a group investigation on this subject, which, through their coordinated efforts, promises to produce highly illuminating and instructive results.

In cases of asthma, which are thought to be due to inhalation of spores of fungi, the use of filtrates hypodermically is of distinct benefit to the patient in most instances if skin testing definitely indicates that the responsible allergin is a mold. The degree of hypersensitiveness exhibited by the patient to a given species of mold may be quite marked, and this must be taken into account in using mold allergins for treatment. Mixed filtrates or extracts made from more than one species of fungus may be utilized if hypersensitivity to more than one species is demonstrated by skin tests. The protein or allerginic substance within the fungus and its spores is liberated by grinding or by fragmenting prior to being extracted with a fluid menstruum which produces a therapeutically effective filtrate. The dosage and frequency of administration of such extracts is determined by the degree of local reaction which they produce, when used for skin testing, as well as by the constitutional response which occurs following their hypodermic injection. Fungous extracts, to be of the highest therapeutic effectiveness, should be made from mature cultures in which full sporulation has taken place.

REFERENCES

1. Alvarez, Ruth Stone: A Red Torula as the Cause of a Tongue Abnormality. Report of a Case. J. A. M. A. 87:1358, 1926.
2. Association of Allergists for Mycological Investigation — quoted by Pennington.
3. Bakst, Henry J., Hazard, J. B., and Foley, John A.: Pulmonary Moniliasis. J. A. M. A. 102:1208 (April 14) 1934.
4. Barnard, James H.: Monilia Albicans in Chronic Bronchial Asthma. Med. Record. 139:534 (May 16) 1934.
5. Bernton, Harry S.: Asthma Due to a Mold — Aspergillus Fumigatus. J. A. M. A. 95:189 (July 19) 1930.
6. Brown, Crofton Tyler: Sensitization to Fungi. Ann. Int. Med. 6:665 (Nov.) 1932.
7. Cadham, F. T.: Asthma Due to Grain Rusts. J. A. M. A. 83:27 (July) 1924.

8. Castellani, Aldo: Fungi and Fungous Diseases. Arch. Dermat. & Syph. 16:383, Oct.; 16:571, Nov.; 16:571, Dec., 1927. Adolph Gehrmann Lectures, University of Illinois, 1926.
9. Castellani, Aldo: Bronchomycosis Which May Simulate Pulmonary Tuberculosis. Am. Rev. of Tbc. (Nov.) 1927.
10. Castellani, Aldo: Observations of Fungi Found in Tropical Bronchomycosis. Lancet, London. 1:13 (Jan. 6) 1912.
11. Clerf, Louis H., and Bucher, J.: Blastomycosis of the Larynx. Ann. Otol. Rhin. and Laryng. 45:923 (Dec.) 1936.
12. Cobe, H. M.: Asthma Due to a Mold. J. Allergy. 3:389 (May) 1932.
13. Cox, Alvin J., and Smith, Charles Edward: Arrested Pulmonary Coccidioidal Granuloma. Arch. Path. 27:717 (April) 1939.
14. Credille, Barney A.: Report of Case of Bronchial Asthma Due to Molds. J. Michigan M. Soc. 32:167 (Mar.) 1933.
15. Davis, A. H., and Warren, E. L.: Pulmonary Moniliasis. Report of Fatal Case. J. Lab. & Clin. Med. 22:687 (April) 1937.
16. Decker, John J.: Pulmonary Moniliasis. New Eng. J. Med. 220:626 (April 13) 1939.
17. Dennis, F. L.: Blastomycosis of the Upper Respiratory Tract, with Report of a Case Primary in the Larynx. Ann. Otol. Rhin. and Laryng. 27:571, 1918.
18. Downing, E. D.: A Case of Blastomycosis with Laryngeal Involvement. J. A. M. A. 70:85, 1918.
19. Farness, O. J.: Bronchopulmonary Moniliasis. Southwestern Med. 22:41 (Feb.) 1938.
20. Feinberg, S. M.: Asthma and Allergic Rhinitis from Molds. Journal-Lancet. 57:87 (March) 1937.
21. Feinberg, S. M.: Mold Allergy. Wisconsin M. J. 34:254 (April) 1935.
22. Feinberg, S. M.: Seasonal Hay Fever and Asthma Due to Molds. J. A. M. A. 107:1861 (Dec. 5) 1936.
23. Flood, Charles A.: Observations on Sensitivity to Dust Fungi in Patients with Asthma. J. A. M. A. 96:2094 (June 20) 1931.
24. Foltz, P.: Anatomicopathologic Alterations of the Lung Due to Monilia. (Candida) Gior. d. r. Accad. di Med. di Torino. 96:45 (April-June) 1933.
25. Foster, John H.: Personal Communication.
26. Fraenkel, E. M.: Molds and Asthma. Brit. M. J. 2:68 (July 9) 1938.
27. Gill, W. D.: Mycotic Infections in Otolaryngology. Texas State J. Med. 31:272 (Aug.) 1935.
28. Gill, W. D.: Torula Mycosis in Man with Special Reference to Involvement of the Upper Respiratory Tract, with Case Reports. Tr. Am. Laryng. Rhin. and Otol. Soc. 40:247, 1934. Also Ann. Otol. Rhin. and Laryng. 44:702 (Sept.) 1935.
29. Greer, A. E.: Fungous Infections of Lungs. Texas State J. Med. 33:750 (Mar.) 1938.
30. Gunter, R. A.: Pneumonitis Due to Mixed Spirochetal and Mycelial Infections. Med. Bull. Veterans Admin. 14: 184 (Oct.) 1937.
31. Hopkins, J. G., Benham, R. W., and Kesten, M. B.: Asthma Due to a Fungous Alternaria. J. A. M. A. 94:6 (Jan. 4) 1930.
32. Ikeda, Kano: Bronchopulmonary Moniliasis. Arch. Path. 22:62 (July) 1936.
33. Ikeda, Kano: Monilia Infection of the Lungs. Am. Clin. Path. 7:376 (Sept.) 1937.
34. Jackson, C.: Blastomycosis of the Larynx. Arch. Otolaryng., Chicago. 3:99, 1926.
35. Jacobson, H. P., Schamberg, J. F., and Morrow, Howard: Fungous Diseases: A Clinico-Mycological Text. Baltimore, Charles C. Thomas, 1932, 1st Edition, p. 253.
36. Keiper, T. W.: Studies on Yeastlike Fungi Isolated from Pulmonary Disease (Bronchomoniliasis). J. Lab. & Clin. Med. 23:343 (Jan.) 1938.
37. Kovnat, Maurice, and Mezie, Cornelius: Streptothricosis. J. A. M. A. 99:2021 (Dec. 10) 1932.
38. Lamson, R. W., and Rogers, E. L.: Skin Hypersensitivity to Molds. J. Allergy. 7:582 (Sept.) 1936.
39. Looper, Edward A.: Mycotic Infections Found in the Trachea and Bronchi. Ann. Otol. Rhin. and Laryng. 45:1153 (Dec.) 1936.
40. McBurney, Ralph, and Searcy, Harvey B.: Otomycosis: An Investigation of Effective Fungicidal Agents in Treatment. Ann. Otol. Rhin. & Laryng. 45: 988 (Dec.) 1936.
41. Macfarlan, Douglas: The Clinical Aspect of Oral Mycology. Laryngoscope. 44:29 (Jan.) 1934.
42. Martin, Donald S., and Smith, David T.: The Laboratory Diagnosis of Blastomycosis. J. Lab. and Clin. Med. 21:1289 (Sept.) 1936.

43. Martin, Donald S.: Complement Fixation in Blastomycosis. J. Infect. Dis. 57:291 (Nov.-Dec.) 1935.
44. New, G. B.: Blastomycosis of the Larynx. Ann. Otol. Rhin. and Laryng. 37:240 (March) 1938.
45. Pennington, Edna S.: A Study of the Incidence of Air-Borne Molds and Skin Sensitivity to Molds. South. M. J. 33:931 (Sept.) 1940.
46. Penta, Arthur Q.: Fungous Diseases of the Lungs. Journal-Lancet. 55:131 (March) 1935.
47. Penta, Arthur Q.: Ibidem.
48. Philibert, A., and Cordey, F.: A New Pulmonary Mycosis Simulating Tuberculosis Due to the Saccharomyces Granulatus. Bull. et Mem. Soc. Med. d. hop. de Paris. 48:1644 (Nov.) 1924.
49. Prince, H. E., Selle, W. A., and Morrow, Marie: Molds in Etiology of Asthma and Hay Fever. Tex. State J. Med. 30:340 (Sept.) 1934.
50. Robinson, George H., and Grauer, Robert C.: Use of Autogenous Fungous Extracts in Treatment of Mycotic Infections. Arch. Dermat. and Syph. 32:787 (Nov.) 1935.
51. Sartory, A., Peteges and Claoue: Laryngite Chronique Psedotuberculeuse d' Origine Mycosique du a Une Levure Nouvelle — Cryptococcus Laryngitidis. N. Sp. Compt. Rend. Soc. de Biol., Paris. 89:179, 1923.
52. Smith, David T.: Oidiomycosis of the Lungs. J. Thoracic Surg. 3:241 (Feb.) 1934.
53. Smith, David T.: Diagnosis and Treatment of Common Fungous Infections of the Lungs. Nat. Tuberc. A. Tr. 29:76, 1933.
54. Smith, David T.: Ibidem.
55. Smith, Leslie M., and Lewis, Geo. M.: Deep Mycotic Infection Caused by Monilia Negra. South M. J. 29:1067 (Nov.) 1936.
56. Smith, Leslie M., and Lewis, George M.: Ibidem.
57. Stevenson, H. N.: Mycotic Infections of the Maxillary Sinuses. Arch. Otolaryng. 20:340 (Sept.) 1934.
58. Stovall, W. C., and Greely, H. P.: Bronchomycosis: A Report of Eighteen Cases of Primary Infection of the Lungs. J. A. M. A. 91:1346 (Nov. 3) 1928.
59. Swartz, Jacob H.: Treatment of Fungous Infections with Ethyl Iodide Inhalations. A Review. Arch. Dermat. and Syph. 40: 962 (Dec.) 1939.
60. Talice, R. V., and MacKinnan, J. E.: A Study on Some Monilia in the Sputum. Bol. Inst. de Clin. quir. Buenos Aires. 4:502, 1928.
61. Towney, John W., Sweaney, Henry C., and Huron, Willis H.: Severe Bronchial Asthma Apparently Due to Fungous Spores Found in Maple Bark.
62. Underwood, George R.: Importance of Fungous as Cause of Asthma in Nebraska. Nebraska M. J. 20:400 (Oct.) 1935.
63. Vadala, A. J.: Myoctic Infection of the Bronchopulmonary Tract. Ann. Otol. Rhin. and Laryng. 49:291 (June) 1940.
64. Van Leeuwen, W. S., Bien, Z., Kremer, W., and Varekamp, M.: On the Significance of Small Spore Species of Aspergillus (Aspergillus Fumigatus for the Etiology of Bronchial Asthma). Zeitscher. four Immunitatsforschung und Exp. Therap. 44:1, 1925.
65. Van Leeuwen, W. S.: Bronchial Asthma in Relation to Climate. Proc. Roy Soc. Med., London. 17:19, 1923-1924.
66. Weidman, F. D.: Cutaneous Torulosis South. M. J. 26:851 (Oct.) 1933.
67. Wittich, F. W., and Stakman, E. C.: Case of Respiratory Allergy Due to Inhalation of Grain Smuts. J. Allergy 8:189 (Jan.) 1937.

DISCUSSION

FRENCH K. HANSEL, M.D., St. Louis: Doctor Gill's report emphasizes the importance of recognizing mycotic infections and differentiating them from other bronchopulmonary conditions. As far as the diagnosis and treatment of respiratory diseases are concerned, cytologic studies of the bronchial secretions as well as cultures should be made. It is noteworthy that mycotic organisms grow well in an acid medium. In the presence of infection of the nose and paranasal sinuses, as well as in the bronchi, a neutrophilic cytologic picture is associated with a low or acid *p*H. In some instances it is important to differentiate between asthma and mycotic infections. In uncomplicated asthma, the bronchial secretion is strikingly eosinophilic, and the secretion is alkaline or presents a high *p*H. These conditions are unfavorable for the growth of mycotic organisms; therefore, this type of infection is rare as a complication of asthma.

On the other hand, hypersensitiveness to fungi in allergy of the nose and sinuses and in asthma is not uncommon. In certain geographic localities, atmospheric fungi may play a part. Such organisms as Alternariae, Aspergilli, Moniliae, rusts, and smuts are the most important. Among workers in flour and grain mills and farmers, sensitivity to fungi is

much more common. Positive skin reactions usually are elicited and response to treatment by avoidance or injections of fungus or extracts from grain dust is generally satisfactory.

Although infection and hypersensitiveness may be associated, it is usually a question of one condition or the other.

T. E. CARMODY, M.D., Denver: It seems a mistake to call on me to discuss this subject because I know so little about it in comparison with Doctor Gill's knowledge of it. I see very few cases of mycotic infection in our part of the country. At least, that is what I did think originally. However, recently I have found a number of cases that had previously been overlooked.

I think Doctor Gill's method of laboratory technic is very good. I feel that we have not kept our cultures long enough to find the mold in many cases. I find and treat aspergillosis fairly frequently in patients after they have been swimming, and that is the extent of the treatment of fungous infections by many of the practitioners in our neighborhood.

However, I do see fairly often actinomycosis, and use the method of diagnosing that with the aid of sulphur granules as Doctor Gill has mentioned. I also see patients who have Moniliae in the mouth.

As for the bronchiogenic condition, I find that especially in bronchiectasis. I also find in many of these cases a contaminant of Vincent's organism. In these cases quite frequently the administration of sodium bicarbonate and bismuth is of value, and it really eradicates the contaminant.

Cases of actinomycosis I have treated with both iodine and x-ray therapy, and the combination of the two very frequently helps.

Doctor Gill spoke of the fact that some people cannot tolerate iodine. I remember that some years ago I prescribed potassium iodide in treating a case of this kind. One of our older practitioners, who knew more about giving iodine than I, advised me to change from potassium iodide to Lugol's solution. We all know that Lugol's solution contains quite a bit of potassium iodide. In this case, I gave eighty ounces of Lugol's solution before a cure was effected.

From the allergic standpoint, I have had very little experience with the treatment of asthma, but from what Doctor Gill has reported and Doctor Hansel has stated, it is important.

I think that in taking biopsies in any of these cases, whether from the bronchus, the larynx, the mouth, or the nose, electrical coagulation is important, or at least some coagulant is necessary. In my opinion, electrical coagulation is much better than anything else for sealing off the lymphatics.

JOHN J. SHEA, M.D., Memphis: The laboratory diagnostic methods of isolating the offending fungus are very unsatisfactory in the type of patient referred to by Doctor Gill. Of late, we have accepted the results of the allergic tests on patients with the various fungi as a practical means of identifying them.

Mr. A. B. S., aged 50, presented himself with the chief complaint of a persistent sore throat of three months' duration, which had resisted treatment. Examination revealed an extensive ulceration of the naso-pharynx and pharynx. The lesion was not limited to lymphoid tissue. The Wassermann reaction was negative. Isolation of the offending fungus was unsatisfactory. The hemogram was as follows: Hemoglobin 91 per cent, erythrocytes 4,390,000, lymphocytes 7,650, small lymphocytes 6 per cent, neutrophiles 94 per cent (juveniles 8, stabs 21, segmented 65). The sensitivity tests to fungi were reported by Doctor John P. Henry as positive to the following:

> Oidiomycin plus one and trichophytin plus three. Biopsies from the uvula and tonsil were reported as follows: (Permanent section) — The capsule consisting of intact surface epithelium is fairly well limited. In one portion the normal lymphoid elements predominate, while in others there is considerable cellular infiltration, consisting of plasma cells and polys. There is one giant cell of the foreign body type.

Physical examination confirmed the opinion that both lungs were extensively involved. This opinion was also confirmed by a roentgenogram, which showed an extensive mottling of the upper three-fourths of the lung fields on both sides with the greatest concentration at the upper lobes. A series of three contiguous excavations were present in the first interspace on the left. There was evidence of small, hard, decreased densities which were becoming confluent in appearance. The film represented a case of typical fungus infection of the lungs. Medication was prescribed which consisted of the usual hemotopoietic stimulants and vitamins. Twenty grains of benzoate were given intravenously

daily with doubtful value. The patient continued to grow weaker and died. An autopsy was not obtained.

Mr. W. B. McC., aged 46, was referred for a biopsy of a persistent leucoplakia of the right pharyngeal wall. The laboratory examination did not reveal the presence of a neoplasm. Because of a past luetic history, the lesion was treated with thorough antiluetic therapy. The lesion continued to spread, and when the patient was seen on June 25, 1940, the lesion extended over both tonsils, uvula, nasopharynx, larynx, and down into the trachea. A roentgenogram of the chest revealed rather marked accentuation of the hilar shadows on both sides and a generalized increase in the peribronchial markings of both lower lobes, more marked on the right than the left. There was considerable peribronchial fibrosis on each side, and from the radiograph the condition was suggestive of a fungous infection. A laboratory study of the discharge was made by Doctor I. D. Michelson of the University of Tennessee. The fungus which was isolated proved to be Monilia albicans. The chief bacteria grown were Proteus, Staphylococcus aureus, and Streptococcus hemolyticus. For this the throat was irrigated with 1 per cent solution of acetic acid. The lesion continued to invade deeper following which there was destruction of the uvula and a V-shaped section of the soft palate. The lymphoid tissue became less resistant, and the tonsils sloughed readily. Supportive treatment included the intravenous administration of 5 per cent glucose. Potassium iodide, thymol, and sodium benzoate were administered. The lesion is clearing up, and we are hopeful that the patient will continue to improve.

I recommend the use of sodium benzoate in preference to iodides or thymol. It has been proven, in regulating diets which include ketchup, that individuals can tolerate more sodium benzoate than they can any other type of antiseptic for mycotic infections. A teaspoonful of sodium benzoate in powder form is prescribed to be taken during a day, the amount to be apportioned into three doses. In my opinion, it is the most effective antiseptic for mycotic infections of the throat.

SIMON HARRY RATNER, M.D., Pittsburgh: This subject is extremely interesting. I particularly observed one remark which Doctor Gill made to the effect that respiratory mycosis in many cases becomes a bronchoscopic problem.

A case of interest was that of a patient whom I saw about five years ago. He was cyanotic and had an intractable, dry, hacking cough, but he did not expectorate. He had a slight septic temperature. The patient gave a history of having had ulcerative stomatitis two or three months previous to admission. We had difficulty in making a diagnosis because the x-ray films revealed normal findings throughout the lungs.

Finally, after having carried out every other means of examination feasible, we introduced a bronchoscope. The bronchoscopic findings were interesting in that the entire trachea and the bronchi were perfectly clean, smooth, and dry. However, in the extreme lower portion of the lobe there was a small amount of secretion. This was aspirated, and the culture revealed Monilia albicans, which has been proven to be pathogenic to patients by means of inoculation and also by skin tests. About a week following bronchoscopy, an x-ray examination of the lungs revealed lesions of the larynx typical of infection produced by Monilia albicans. In this case, apparently the lesion was pneumonitic and not due to bronchitis, as Castellani so often has described.

In line with Doctor Carmody's remarks, it was interesting to note that this patient was unable to tolerate potassium iodide, but he got along well with Lugol's solution. He made a complete recovery.

WILLIAM D. GILL, M.D., San Antonio: (Slide.) This is a photomicrograph of a culture of Torulae, showing the budding forms. You will notice the arrows pointing to the little daughter cells breaking away from the sides of the parent cells.

(Slide.) Next is a photomicrograph of the Penicillium on one side, and on the other side the Aspergillus, made from a slide culture.

(Slide.) Here is shown a method of making a slide culture. The nutrient medium is inoculated with the suspected material, put on a clean cover slip, and is supported by two strips of dental wax. The cover slip is placed on a slide. The growth takes place along the free edge of the cultural medium, appearing in from one week to two or three weeks and lends itself readily to microscopic study.

(Slide.) This is a sketch showing a mycotic infection involving a tonsil. Possibly all of you have encountered this condition. It is relatively harmless, but difficult to eradicate. It is due to the Streptothrix.

(Slide.) This represents an aspergillus infection in the dorsum of the tongue and anterior pillar. I was unable to get a photograph. This is an artist's drawing.

(Slide.) Here is a photograph showing an opalescent, milky patch on the posetrior pharyngeal wall. This appeared in the case of a medical student and was due to a Monilia. It disappeared promptly under local application of Lugol's solution.

(Slide.) This shows a blastomycotic lesion on the hand of a woman about fifty-odd years of age. There is another lesion on the leg and in the faucial and tonsillar areas.

(Slide.) This lesion occupies a wide area on the dorsal portion of the tongue in a young woman supposedly subject to pulmonary tuberculosis. It is a filamentous lesion, black in color, from which a chromogenic Torula was isolated. By local applications of iodine, followed by tincture of benzoin and the use of an autogenous vaccine, the suspected pulmonary tuberculosis cleared up as did also the tongue lesion.

(Slide.) This is a retouched drawing, showing a blastomycotic lesion on the side of the tongue and also the buccal mucosa.

(Slide.) This is a torulosis of the left tonsil. You will notice the typical scooped-out appearance of the lesions.

(Slide.) Shown here is a torulous lesion on the hard palate, which occurred in a woman during pregnancy. The Torulae were also isolated from the urine on several occasions.

One thing with regard to torulous lesions which I have seen which impresses me is that the amount of redness that one expects to find associated with that type of inflammatory reaction is very slight, but the degree of pain that accompanies the lesion is intense and out of all porportion to the size of the lesion.

(Slide.) Showing a blastomycotic orbital abscess, secondary to toruliform infection of the ethmoidal sinuses.

This shows the drainage area the second day after operation. The child was seen some time around 1928, and about a year ago she walked into my office just to say "hello" to me. She is a young lady now and shows no permanent after-effect of the former illness.

(Slide.) This is a case of actinomycosis. It is the only one I have that could be included in the series. The case was seen in 1924. The area of infection was present around a molar tooth on the same side. The entire side of the face was involved, and you will notice the fistulous openings on the side of the face and eyelids. The patient recovered.

(Slide.) This is from a fatal case of torulosis. You will notice the thickened region at the base of the brain, and in this area numerous budding forms are present.

Incidentally, torulosis is to be suspected in all cases where the percentage of lymphocytes in the spinal fluid is found to be abnormally high, as often the Torulae are confused with lymphocytes.

(Slide.) This is a photomicrograph, showing cerebral tissue and great thickening of the pia and arachnoid with marked vascular engorgement.

(Slide.) This a photomicrograph, showing budding forms and cells that are about to separate. This is another budding form. Here is one with a little daughter cell on the side.

(Slide.) This is from a fatal case of coccidiosis. You can see the Coccidioides appearing in budding form in the cerebral tissue.

(Slide.) This is a case of sporotrichosis of the thigh. The patient had pulmonary involvement.

(Slide.) This represents a case of pulmonary sporotrichosis. There is nothing characteristically representative of mycotic infection.

(Slide). This is pulmonary moniliasis. The chief involvement is in the hilus region and lower right lobe of the lung.

(Slide.) This represents another case of pulmonary aspergillosis.

In closing, I wish to emphasise the necessity of careful study to avoid overlooking infections of this type, as many lives can be saved by early diagnosis. I further wish to thank my colleagues who have made this investigation possible through their whole-hearted cooperation and helpful advice. Those who have so generously consented to discuss this paper have added greatly to its value by their remarks, and I wish to thank them for the time and effort they have put forth in the liberal discussions which they have given this subject.

GRANULOMATOUS ULCER OF THE NOSE AND FACE OF UNKNOWN ETIOLOGY — USUALLY PROGRESSIVE, GANGRENOUS AND FATAL

WALTER B. HOOVER, M.D.
BOSTON

THIS PRESENTATION will consist of a short review of the literature on the subject described by the above title and a report of four cases which have been treated by personal acquaintances or by myself. A fifth case is mentioned which closely resembles the fatal cases. It is hoped that this study will stimulate interest and possibly lead to further research in this country concerning the etiology of the disease.

REVIEW OF LITERATURE

Fatal granulomatous ulcerations of the nose and face have been described under various titles. In 1896 Peter McBride[9] described a "Case of Rapid Destruction of the Nose and Face." H. Macnaughton Jones[6] the following year described a case of "Esthiomenic Menstrual Ulcer of the Nose." In 1906 John A. Fordyce[4] presented "A Case of Undetermined Tropical Ulcer Involving the Nose, Pharynx and Larynx, with Histological Findings." In 1914 David Nabarro[10] discussed "An Obscure Case of Ulceration of the Nose in a Child Simulating an Epithelioma." In 1921 Sir Robert Woods[14] described two cases of "Malignant Granuloma of the Nose." In 1925 G. A. D. M'Arthur[8] described another such case. In 1929 L. Chatellier[3] reported a case of "Sarco-Lupus Pernio, Mutilant et Mortel." In 1931 I had the pleasure of listening to Dr. G. B. Wood,[13] of Philadelphia, present his case of "Mutilating Granuloma of the Nose and Face, with Fatal Ending," before the American Laryngological Association. This is the first American case reported. His report was so complete that I have little to add.

In 1933 J. P. Stewart[12] reported upon "Progressive Lethal Granulomatous Ulceration of the Nose." He added four unreported cases and carefully reviewed the literature and included eight cases which previously had been reported. He considered the cases of Jones,[6] Fordyce[4] and Nabarro[10] to be slightly atypical. Stewart[12] also discussed differential diagnosis and allied conditions. His paper should be read by anyone interested in this subject.

In 1936 Erich Joisten[5] reported two cases, "Zwein Ätiologisch Unklare Fälle von Gagränescierender Entzündung der Nase und des Oberkiefers." He reviewed the literature, citing Berendes[2] who collected sixteen cases from the German literature, nine from the English literature, and one each from the French, Japanese and Italian literature.

H. G. A. Bayer,[1] in 1937, and Walter Schütz,[11] in 1938, reported cases under similar German titles. Alfred Lewy,[7] of Chicago, reported the second American case in a girl of eleven years, under the title, "A Case of Gangrenous Osteomyelitis of the Paranasal Sinuses." F. Wegener[15] reported three cases with autopsy studies, in 1939. He discussed the pathologic findings and etiologic possibilities.

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

Department of Ear, Nose and Throat, The Lahey Clinic, Boston.

REPORT OF CASES

CASE 1. — A man, aged fifty-one, a private patient of Doctor Knowlton, came to him August 8, 1936, complaining of a swelling of the right side of the nose and face, and of fever. The present illness began in November, 1935, at which time he began to have stuffiness of the nose and right frontal headaches with a sense of tightness over the area of the right antrum; the headache was present on awakening in the morning and increased throughout the day. At the onset there was a little mucoid discharge. The obstruction, however, became marked, and treatment with sprays did not relieve the condition.

Treatment consisting of electrocoagulation to the turbinates did not give relief, and it was necessary for him to sit up or have his head propped up in order to sleep. The patient's teeth were said to be in poor condition, and all of them were extracted throughout the winter and spring. By April 24, 1936, he felt much better. The headache was relieved, and there was some improvement in the stuffiness of the nose. He was well until June 12 when severe headache and generalized pains in the muscles and joints developed which were accompanied by chills and a rise in temperature to 105° F. At this time he entered a local hospital. His temperature receded within eight days, but fever developed again after two days of normal temperature, and his course remained septic. During his stay in the hospital a puffiness developed beneath the right eye which later receded.

About July 10 swelling and tenderness were again noted along the right side of the nose; there was no nasal bleeding and only a moderate amount of nasal discharge. His appetite which had been fair was poor following the chill in June, and at times there was nausea with occasional vomiting. The patient entered the Massachusetts General Hospital August 8 for study and treatment. Smears, cultures, blood cultures, blood studies, and studies for fungal infection were done. On August 14 Doctors Knowlton and Fred explored the right antrum. It contained pus and polypoid membrane which were removed. Specimens for biopsy were taken from the inside of the right ala, the right ethmoid region, the septum, and from the external surface of the nose. At this time there was swelling and tenderness of the nose and face, with an ulcerated area and perforation through the right lateral wall of the nose extending slightly on the cheek. His temperature ran a septic course from normal to 106° F., remaining for the most part between 103° and 104° F. He had only moderate pain. He was strong enough to be up, and he felt surprisingly well considering the rise in temperature and the septic course. Roentgenographic reports of his chest revealed findings entirely within normal limits.

Roentgenograms of his sinuses showed soft tissue in both ethmoids and fluid in the right antrum, but no osteomyelitis. The blood studies showed the Wassermann and Hinton tests to be negative on two occasions and the Widal test and blood cultures to be negative on several occasions. The leukocyte count varied from 5,600 to 12,600. The differential count varied as follows: Polymorphonuclear cells, 60 to 73 per cent, and lymphocytes, 27 to 33 per cent, with only a small number of monocytes and eosinophil cells. The hemoglobin varied from 60 to 72 per cent. Examination of the spinal fluid revealed normal cells and protein. The spinal fluid Wassermann and Hinton tests were negative. The specimen taken for biopsy revealed granuloma consistent with late syphilis. A second specimen for biopsy was taken August 26, and again nothing new was found on study of these sections. Study

of the cultures showed a predominance of diphtheroids, Staphylococci and Streptococci, with both hemolytic and nonhemolytic Streptococci. Practically a pure culture of Staphylococci was obtained from the pus from the antrum. The smear and cultures were negative for fungus and acid-fast organisms. Some gram-positive bacilli and gram-positive diplococci were found, possibly pneumococci. The blood cultures all gave negative results. A search for malarial parasites was fruitless.

Treatment consisted of a diet high in vitamins and caloric value, cleansing of the wound with potassium permanganate (1:10,000) irrigations, and packs consisting of copper sulphate and solutions of chlorinated soda and acriflavine. Infra-red heat to the area was administered daily. Quinine was given in large doses for four days, without effect. This was discontinued, and potassium iodide was given in doses up to 90 grains a day.

In spite of the best local and general care that could be given, his condition rapidly became worse, with extension of the lesion and a continued high fever. Near the end of his hospital stay, two transfusions were given, with no apparent benefit. His pulse rate varied from 80 to 160, his respirations from 20 to 40, and his temperature from normal to 106° F. He died as the result of a massive hemorrhage on September 30, 1936, eleven months after medical treatment had been started.

CASE 2. — A man, aged thirty-five, was admitted to the Massachusetts Eye and Ear Infirmary September 4, 1937, with the chief complaint of swelling of the right side of the face. The present illness began approximately in the early part of February, 1937, with swelling of the right side of the face and a thin nasal discharge which later became foul. He was treated by his physician, but the swelling of the face persisted and the foul nasal discharge became more marked. The postnasal discharge had been of considerable concern to him because it had caused a loss of appetite and with this he lost weight to the extent of 25 pounds before being admitted to the hospital. He had become too weak to carry on work and two weeks previous to admission had had some pain on swallowing and also a slight cough.

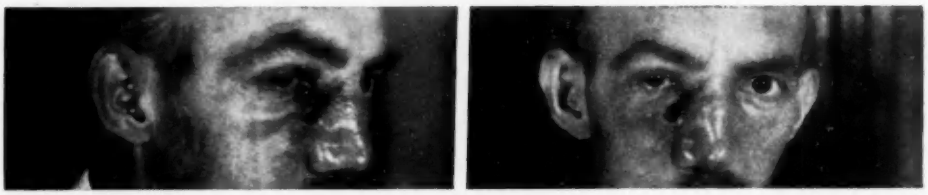


FIG. 1. Case 2. Demonstrating an ulcer in region of the right lacrimal sac with fistula into the nasal cavity.

His past history revealed influenza in 1917; he could not remember any illness since that time. He was married. His wife and two children were well.

The patient's general physical examination, other than emaciation and loss of weight, was negative. The heart and lungs were normal. Examination of the face showed a hard, brawny, reddened and tender area over the frontal process of the maxilla of the right side, with some ulceration and a draining fistula. (Fig. 1.) The anterior half of the nasal septum was destroyed, and the nose and nasal chambers were covered with heavy crusts and foul pus. Examination of the

mouth revealed tenderness of the gums on the right side and the teeth in bad repair. Postnasally, there was marked purulent discharge, and the tonsils were reddened. The anterior cervical glands were palpable.

Laboratory and roentgen examinations were as follows: Roentgenograms of the sinuses revealed right pansinusitis. X-rays of the teeth showed apical abscesses of the right central incisor and left upper second molar. The blood studies showed the Wassermann and Hinton tests to be negative; blood sugar and nonprotein nitrogen to be normal; hemoglobin to vary between 80 and 64 per cent; erythrocyte count 3,350,000; leukocyte count, 9,100; differential count, 74 per cent polymorphonuclears and 26 per cent lymphocytes.

Smears from the lesion were negative for tubercle bacilli and Vincent's organisms, but gram-positive diplococci were present. Both aerobic and anaerobic cultures showed Staphylococcus aureus. The blood cultures were sterile. Cultures for fungi were negative. A specimen taken for biopsy showed acute and chronic inflammation. Examination of the bone revealed acute and chronic osteomyelitis. Examination of the urine revealed normal findings.

Treatment consisted of nasal irrigations, hot poultices, oil sprays, packing the wound with urea, and application of copper sulphate. Both arsphenamine and tartar emetic were given in a trial treatment, without effect. Dental extractions of the abscessed teeth and mouth hygiene were carried out. The temperature varied between normal and 104° F., pulse rate between 70 and 125, and respiration between 20 and 28.

In spite of treatment and further care after discharge from the hospital, the patient died on December 11, 1937.

Case 3. — A man, aged fifty-seven, a stone cutter by trade, was referred to the Lahey Clinic by Dr. M. S. Twitchell on January 24, 1938, because of nasal obstruction and swelling and ulceration of the nose. His history was very interesting in that in 1915 a specimen for biopsy was taken from a granuloma on the right side of the nose; the microscopic report showed the tissue structure to be that of an infectious granuloma with small necrotic areas scattered throughout the mass. Tubercle bacilli were not found. He was treated with old tuberculin. This granuloma healed completely, and the patient was well without any disability or disease that he could recall until the spring of 1937. In April of 1937 the nasal obstruction became more marked, and there was a thin nasal discharge. He was treated by a competent rhinologist, without improvement. In August his nasal obstruction was much more severe, and he began to run a temperature ranging from 100° to 102° F. A portion of the turbinates was removed to relieve obstruction, without success, and a specimen for biopsy was taken by his rhinologist, which showed chronic inflammation without evidence of malignancy.

The lesion progressed in spite of treatment, the discharge became bloody, and crusting in the nose became severe. On September 14 a second biopsy was taken. Microscopic examination of the specimen again showed chronic inflammation. The temperature rose to 103° and 104° F. He changed physicians on October 25, at which time there was marked crusting of the left nasal cavity near the anterior end of the left middle turbinate where bare bone was present. There was indurated tissue about the area of ulceration, and externally there was swelling and a marked dusky redness of the nose, associated with edema of the lower left eyelid.

Roentgen examination of the sinuses at this time showed them to be clear. Roentgenograms of the chest revealed

moderately advanced silicosis without evidence of accompanying tuberculosis. The specimen for biopsy at this time consisted largely of necrotic and inflammatory tissue, and many blood vessels were scattered in this mass, some with thick walls, but the endothelial cells were uniform in size and shape. No atypical epithelial cells of any type were found, and there was no evidence of malignancy. A diagnosis could be made only of inflammatory granuloma. Tubercle bacilli could not be found in the sputum. Several Wassermann tests were negative. Two x-ray treatments were given, with temporary improvement, and they were followed by injections of tuberculin (Parke, Davis) every fifth day.

The first week in December the swelling and redness in the nose increased, and some ulceration appeared on the surface. X-ray treatments were again given without benefit and were discontinued on December 20. In spite of the several negative Wassermann tests, active antisyphilitic treatment was given with bismuth, potassium iodide, and intravenous arsphenamine. The lesion continued to progress, and the antisyphilitic treatment was discontinued January 12, 1938, by which time an opening had formed through the lateral wall of the nose.

(Figure 2.) On January 24, 1938, when I first saw him, he had been admitted to the New England Deaconess Hospital where an effort was made to establish a diagnosis. Roentgenograms of the sinuses and chest again were negative. Blood studies were made and repeated at intervals. The hemoglobin varied from 66 to 80 per cent. The leukocyte count varied from 10,000 to 14,000. The differential count showed a variation of 70 to 80 per cent polymorphonuclear cells and many young forms. The urine examination revealed normal findings throughout. Another biopsy was taken with the same findings as those previously reported. Cultures showed hemolytic Staphylococcus aureus, hemolytic and nonhemolytic Streptococci and diphtheroids which were

FIG. 2 (a), Case 3 — January 24, 1938. Illustrating external ulceration, induration and swelling of the nose and left cheek.

FIG. 2 (b), Case 3 — Same as *a*, lateral view.

FIG. 2 (c), Case 3 — February 19, 1938. Showing enlargement of opening through the lateral wall of the nose.

found to be nonvirulent. Numerous slides and smears were made in an effort to find tubercle bacilli, Lepra bacillus, the bacillus of glanders, yeast, and fungus. These did not yield positive results. Special anaerobic cultures were made and also special media were used for the growing of fungi; these also were negative.

The treatment in the hospital consisted of rest, high caloric diet, high vitamin intake and the administration of iron. The local treatment to the nose consisted of nasal irrigation, hot boric compresses, packing the wound with Staphylococcus bacteriophage, packing off the nasal cavity, filling the wound with sodium perborate powder and a similar treatment with urea crystals. Large doses of potassium iodide were given without improvement, and this was therefore discontinued. A course of treatment with prontylin was given for nineteen days, which the patient tolerated well. Subcutaneous injections of Staphylococcus bacteriophage were given.

It is interesting to note that after the administration of prontylin, Streptococci were fewer in number in the smears and were difficult to culture. The course in the hospital was progressively downhill in spite of the excellent care. He ran a mild septic course as evidenced by the temperature chart. (Fig. 3.)

His appetite remained good, he felt equal to being up and about a little each day, and was allowed bathroom privileges. The bowels were regular. On March 8 he became nauseated, and there was some abdominal distention and evidence of intestinal obstruction. The following day the temperature rose to 106° F., and he died apparently as a result of acute intestinal obstruction. A postmortem examination was refused, but removal of some of the tissue about the area was permitted. This again was studied by the pathologist, but a diagnosis could not be made.

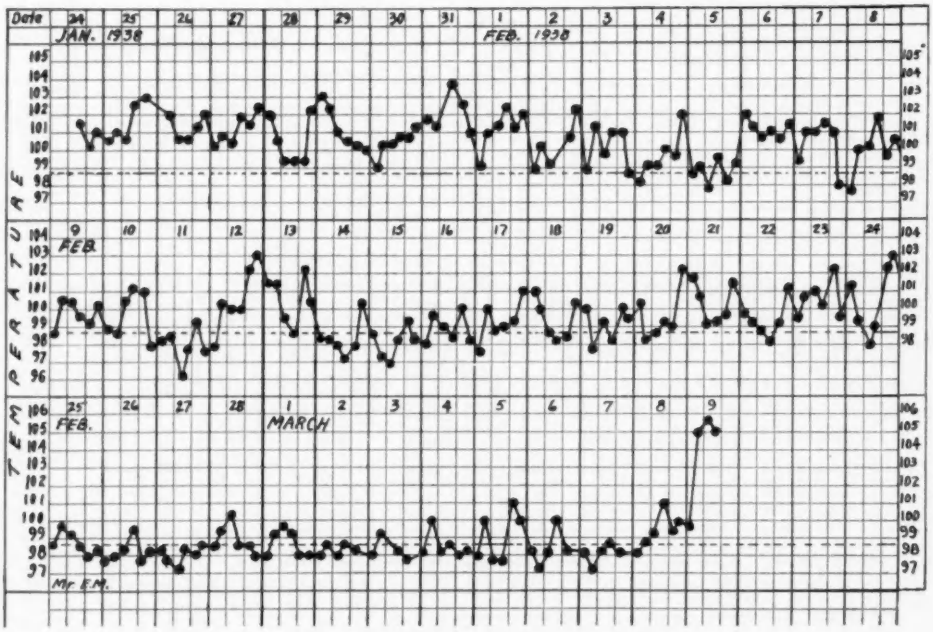


FIG. 3

CASE 4. — A man, aged thirty-six, a worker in a chemical plant, was referred to the out-patient department of the University Hospital, Ann Arbor, Michigan, by Dr. H. M. Pike on January 30, 1939. His past history has two points of interest; (1) he was a worker in a chemical factory, and (2) he had been exposed to toluene. In July, 1937, he had had had stuffiness of his nose for which a submucous resection of the nasal septum was done for relief of obstruction, with apparently complete healing.

In September, 1939, the patient was treated for a postnasal discharge, cough, and crusting in the nose. These symptoms became progressively worse in spite of treatment. On January 31, 1939, the general examination revealed entirely normal findings. Examination showed both nasal chambers to be filled with hard crusts which could be removed only by nasal packing and frequent irrigations. When the crusts were removed, the membranes of the turbinates and septum were found to be largely destroyed. Under observation and treatment, which will be mentioned later, the disease gradually progressed so that by March 16, 1939, the turbinates had been completely destroyed, ulceration had occurred on the hard palate with perforation through into the mouth, and there was marked redness, swelling, and tenderness on the left cheek with a fluctuating area over the inner canthus of the left eye. By this time the temperature had reached 104° F., and the patient was hospitalized. However, hospital care did not alter the progress of the lesion. The cellulitis of the face subsided, leaving a small draining sinus over the lacrimal sac, and the ulcer of the hard palate tripled in size within a month. The borders remained elevated and indurated with surrounding hyperemia. During the first week of May, 1939, the right cheek became swollen. This was followed by erosion of the granuloma through the cheek and the base of the nose, so that by the latter half of May an opening 1 by 3 cm. was present through which could be seen the destroyed bone of the maxilla. The hard palate had been entirely destroyed, and many teeth had loosened from the alveoli and fallen out of the right upper jaw. During the third month of hospitalization the necrosis continued to extend to the cheek, the orbit, the nose and oral cavity, and across to the left cheek. During this time he had an irregular septic temperature, and there was gradual wasting of the tissues of his entire body and emaciation.

Diagnostic studies were carried out, and many blood counts were made which revealed no evidence of a blood dyscrasia. Leukocyte counts ranged from 8,000 to 17,000. The differential counts were always within normal limits. The hemoglobin varied from 92 to 65 per cent. Blood studies for syphilis were negative on four occasions. Five biopsy studies were made which showed marked inflammatory infiltration of lymphocytes and a large number of neutrophils. There were many new blood vessels with high endothelium. The mucous glands showed some atypical hyperplasia. There were no tubercles nor evidence of neoplasm. Extensive necrosis was present. A definite diagnosis, other than an infectious granuloma, was not possible from study of these specimens from biopsies.

The bacteriological examination showed cultures and smears to be negative for fungous infection. On February 2, 1939, a few acid-fast organisms were found, but guinea pig inoculation gave negative results. Further smears for acid-fast organisms were negative, and cultures were negative for bacillus of diphtheria. Agglutination tests for Brucella and the typhoid group were negative. Blood cultures were negative. The tuberculin test was negative for 1:10,-

000 dilution and faintly positive for 1:100 dilution. Consultations were held with members of the medical, general surgical, urological, dermatological, neurological, and radiological departments of the University. The case was followed closely by members of the departments of dermatology and medicine who gave frequent general examinations.

The treatment consisted of a high caloric diet with high vitamin intake. Two blood transfusions were given during April, and the patient was maintained on fluids for the last three weeks of his hospital stay.

Immediately after he was admitted to the hospital, x-ray treatment of 900 r units was given to the ulcer in the roof of the mouth, which seemed to hasten the necrosis. Therefore, further x-ray treatment was not given. Local treatment consisted of irrigations with potassium permanganate, cleansing with sodium perborate and hydrogen peroxide, packing with zinc peroxide, and packing with bacteriophage, all without apparent improvement. Therapeutic tests with bismuth and arsphenamine were made, also without effect. This was followed by a course of sulfapyridine therapy, again without response.

The patient was discharged from the hospital by ambulance on June 22, 1939, and he died June 29. Necropsy was performed which showed chronic myocarditis, an old healed endocarditis, chronic hepatitis, congestion of all organs, marked dehydration, terminal suppurative pneumonia and cellulitis of the face, both right and left cheeks, with extensive necrosis and erosion, and destruction of all of the bones of the upper jaw and face.

COURSE OF THE DISEASE

The onset of a granulomatous ulcer is most insidious, and the patient may complain only of nasal congestion, nasal obstruction, or watery discharge from the nose for several months or even years before ulceration develops. Otherwise, he feels quite well. He may seek relief from nasal obstruction or discharge. In Case 1, here reported, headaches were a predominant symptom. The septum may be straightened (Case 4) and the turbinates either removed (Case 3) or cauterized (Cases 1 and 5) for the relief of the obstruction; the nose may or may not heal from the surgical trauma. Over a period of a few months the nasal symptoms become progressively worse, and the obstruction cannot be relieved. The discharge becomes serosanguineous, brown, or purulent, with a disagreeable odor. Crusts then form which are difficult and painful to remove. When the crusts are removed, ulcerative surfaces are exposed, and slight bleeding occurs.

It is remarkable that this process may be present for a few months with very little reaction in the general condition of the patient. He may feel quite well and have no pain. On the other hand, pain and headaches may be marked symptoms. Usually to remove the crusts causes pain, and pain is usually a troublesome symptom during the late course of the disease.

The disease progresses with baring and necrosis of the bone in the nose. The tissues of the external nose and face become reddened and indurated, and finally a gangrenous ulcer appears on the external surface. An abscess in relation to the lacrimal sac may form and drain, as occurred in two cases (Cases 2 and 4). Similar changes may take place upon the palate and the alveolar margin into the oral cavity. Abscesses may form and drain spontaneously or require drainage. The exposed bone may sequestrate, and the teeth in the involved area may become loosened and fall out (Case 4).

TABLE 1

Case	Age and sex	Date of onset	Duration, months	Previous surgery	Variation					Cause of death
					Pulse	Temperature	Respirations	Hemoglobin	Leukocytes	
1	51 M	11/35	11	Cautery of turbinate	80/160	98/106	20/40	73/60	5,600 12,600	Hemorrhage
2	35 M	2/37	9	None	70/125	98/104	20/28	80/64	9,100	Sepsis
3	57 M	4/37	11	Turbinectomy	70/140	97/106	18/36	80/66	10,000 14,000	Intestinal obstruction
4	36 M	7/37	24	Submucous resection	85/150	98/104	20/32	92/66	8,000 17,400	Inanition Athrepsia Sepsis
5*	40 F	10/38	24	Electro-coagulation Biopsy	70/100	97/100	20	66/80	9,800	Living and well

*Atypical
In all five cases the differential count was normal for infections
In Cases 1, 2, 3 and 4 the urine examination was normal; in Case 5 there were a few leukocytes
In all cases the biopsy specimen showed acute and chronic inflammation

During this active ulcerative stage there may be a mild or even a severe septic temperature which tends to increase. The temperature may vary from normal to 105° or 106° F., and rigors or chills may occur as in Case 1. The patient, however, may feel better than one would expect. A troublesome hemorrhage may take place if the area of an artery is eroded as in Case 1 where death resulted from hemorrhage. Packing or ligation of vessels is indicated when this occurs. The gangrenous granulomatous area may spread and may cover large areas with marked mutilation (Case 4). The temperature usually may remain elevated. The patient may have difficulty in taking nourishment. Fluid may be given parenterally or by tube. The patient finally may succumb to terminal pneumonia, toxemia, inanition or hemorrhage. The entire course of the disease may cover a period of from six months to two or three years. (Table 1.)

ETIOLOGY AND DIAGNOSIS

Since the etiology is unknown, any discussion of etiology is mere conjecture. The more common causes of such progressive ulcerations are tuberculosis, syphilis, new growths, fungous infections, leprosy, glanders, and so forth. (Table 2.) These have been excluded in all cases reported here by laboratory and therapeutic tests.

TABLE 2

DIFFERENTIAL DIAGNOSIS

1. Syphilis
2. Tuberculosis
3. Malignant disease
4. Noma
5. Fungous infections
6. Agranulocytosis
7. Leprosy
8. Glanders
9. Anthrax
10. Myiasis
11. Postencephalitic ulcer (trophic)
12. Leishmaniasis
13. Yaws
14. Diabetic gangrene

The above diseases are ruled out by laboratory procedures, therapeutic tests, and clinical course.

Schütz[11] reported six apparent cases in two of which a lymphosarcoma was found at autopsy, one with metastasis to the kidney and the other with metastasis to the intestinal tract. He stated that it would be easy for a real tumor to

be concealed in a case where the diagnosis of malignant granuloma has been made. However, one can be certain of the diagnosis of malignant granuloma if the blood count shows a mild leukopenia with a marked "shift to the left" in the differential count. Some of the cases reported by him show a moderate increase in the leukocyte count. In lymphosarcoma the leukocyte count is over 11,000 and there is not the "shift to the left," even though there is no increase in lymphocytes.

The most common organisms found in these lesions are Streptococcic and Staphylococcic bacteria and pseudo-diphtheritic bacilli. Because these organisms do not ordinarily produce such progressive gangrenous granulomatous ulcers, a symbiosis has been suggested between them, with the production of a necrotizing substance capable of such destruction.

Stewart[12] quoted Brewer and Meleny's theory of symbiosis between the Staphylococci and Streptococci, while Joisten[5] suggested a symbiosis between the pseudo-diphtheria and other organisms. To date the isolation of organisms from the granuloma and the injection of such organisms into experimental animals has failed to reproduce progressive gangrenous granuloma.

Wegener[15] concluded from his post-mortem studies that Streptococci well may play some part in the etiology of this condition since his cases showed generalized changes in tissue characteristic of severe infection. He also found a marked periarteritis nodosa and felt that the etiology of the two conditions might be related. He further stated that such a periarteritis nodosa was found in virous diseases, such as Rocky Mountain spotted fever and that a virus might be the etiologic factor in this disease.

Members of the pathological department at Ann Arbor suggested that the etiologic factor in Case 4 might be a chemical injury, since this patient was a worker in a chemical factory. They also questioned the possibility of an Arthus phenomenon.

The spontaneous cure noted by Schütz[11] and the apparent cure in a similar case now under my observation suggest an unknown etiologic factor with secondary invasion of pyogenic organisms.

Age and sex. — This disease is most common in young to middle aged patients. Cases are reported in patients from eleven years to sixty-eight years old. Only two cases are reported in children. The sex ratio is about twenty males to one female.

PATHOLOGY

The following description of the microscopic section from Case 4 is given by Dr. Shields Warren. The same description applies to Case 3.

> On the border of the lesion there is an amorphous mass of necrosis beneath which there is infiltration of inflammatory cells (chiefly lymphocytes), macrophages and occasional plasma cells. A few polymorphonuclear leukocytes are also present. There is some new formation of capillaries. The larger vessels in the tissue show a definite perivascular cuff of lymphocytes and macrophages with some regions of degeneration of arterial walls. While there are focal accumulations of the infiltrating cells in the tissues, the lesions are not characteristic of tuberculosis, syphilis, or leprosy. Diagnosis: Chronic granuloma, etiology unknown.

Since Case 5 is atypical and apparently recovering, I am also giving Doctor Warren's description of two sections of tissue from the case, as follows:

> Section 1 shows infiltration of the tissues with closely packed lymphocytes, macrophages and rare plasma cells. Occasional polymorphonuclear leukocytes are present. There is considerable new capillary formation, and there tends to be focal accumulation of the cells about the vessels. Multinucleate giant cells rarely are seen.

Section 2. The mucous membrane is very heavily infiltrated with lymphocytes, macrophages and some plasma cells, which are often diffusely scattered (but sometimes focal) with rare multinucleate giant cells. New formation of capillaries and some fibroblastic proliferation are apparent. Around some of the vessels there is a distinct perivascular aggregation with occasional arteritic infiltration of vascular walls. Some portions of the mucous membrane show pseudotuberculous aggregations of macrophages and lymphocytes with slight peripheral fibrosis. No tubercle or Lepra bacilli are found. Diagnosis: Chronic granuloma, etiology unknown.

In Wood's[13] report of a case the opinions of Drs. Eugene A. Case, Joseph McFarland, James Ewing and Frederick DeF. Weidman are given concerning the microscopic pathology. Certainly we are unable to add anything new.

tissue could not be differentiated from cases which were progressive and resulted in death. J. P. Stewart[12] recorded two cases that did not die as the immediate result of the granuloma.

I have under treatment at the present time a woman forty years of age (Case 5), with a granuloma of the nose. (Figures 4 and 5.) She has had symptoms for eighteen months and has been carefully examined by competent men in two large clinics. All laboratory tests including a biopsy had been done without establishing the etiologic factor. While the patient was under our observation, the granuloma eroded through the dorsal and lateral nasal wall at the junction of the upper lateral cartilages and nasal bone, lifting the skin upward. The granulomatous area was dissected out, the patient was placed on antiluetic treatment, and apparently a cure has resulted. I cannot say that the antiluetic treatment has produced a cure, because repeated blood tests elsewhere and at this clinic have been negative; there is no history even suggestive of syphilis.

FIG. 4. Case 5. April 16, 1940, showing raised area of skin over the granuloma.

FIG. 5. Case 5. Sept. 10, 1940, following the administration of iron, high vitamin intake and antiluetic therapy.

PROGNOSIS

The prognosis usually is hopeless, as indicated by the title of this paper, yet the patient in Case 3 had a granuloma in 1915 from which he recovered. Schütz[11] mentions one spontaneous cure in a case in which the granulation

Such cases suggest that the defense mechanism of the body, at least in some cases, is capable of overcoming the etiologic factor, whatever it may be.

TREATMENT

There is no specific treatment. Surgical excision has been disappointing. Bayer's[1] removal by electrocoagulation gave only a temporary cleansing of the area. Radiation treatment has given temporary improvement in early lesions and was helpful in Case 3. Stewart[12] recommended roentgen ray treatment. This was used in his case which recovered from the granuloma. Roentgenotherapy in the more advanced stages was of no value and seemed to hasten necrosis (Case 4).

Prontylin (or sulfanilamide) has not controlled the disease in cases in which it was used. This drug apparently decreased the number of Streptococci in Case 3, but did not stop the progress of the lesion. Numerous antiseptics have been employed, but all with equally poor results. Staphylococcus bacteriophage seemed to have no effect. (Table 3.)

TABLE 3

	TREATMENT								
Case number	Antiluetic treatment	X-ray	Sulfanilamide	Potassium iodide	Staphylococcus bacteriophage	Transfusions	Urea	Perborate	High vitamin intake
1	+	0	0	+	0	+	0	0	+
2	+	0	0	+	0	0	+	+	+
3	+	+	+	+	+	0	0	0	+
4	+	+	+	+	+	+	+	+	+
5*	+								+

*Atypical

At the present time should I have a case to treat, I would interest a research laboratory, which has the facilities for the study of viruses and for research in bacteriology, to investigate the etiologic factor.

I should interest an internist in keeping the patient's general nutrition in good condition and in supplying all supportive measures possible.

Locally the wound would be kept clean by bland washes and packed with sulfathiazole powder, and some of the sulfanilamide derivatives would be given internally.

I would also give roentgenotherapy.

SUMMARY

A short review of the literature on granulomatous ulcerations of the nose and face has been given. Four new cases of this condition have been reported, together with a fifth case which is atypical. These four cases ran a fairly typical clinical course and apparently constituted a disease entity of unknown etiology, for which at present there is no adequate treatment.

It is my hope to stimulate further interest in the search for the etiologic factors in this disease. Since I have been able to collect four cases from my personal acquaintances, it would indicate that this condition is apparently much more common than the report of only two cases in the American literature would suggest.

In conclusion, I wish to thank Dr. C. D. Knowlton for the privilege of reporting Case 1, Dr. LeRoy A. Schall and Dr. J. C. Drooker, Case 2, and Dr. A. C. Furstenburg and Dr. F. D. Lathrop, Case 4.

REFERENCES

1. Bayer, H. G. A.: Ätiologisch Unklare, Gangräneszierende Erkrankungen des Nasenskeletts. Der Hals- Nasen- und Ohrenarzt., 28:6 (April) 1937.
2. Berendes: Quoted by Joisten.
3. Chatellier, L.: Sarco-Lupus Pernio Muti-

lant et Mortel. Ann. d. Dermatol. et d. Syph., 10:1213 (Nov.) 1929.
4. Fordyce, J. A.: A Case of Undetermined Tropical Ulcer Involving the Nose, Pharynx and Larynx, with Histological Findings. Jour. Cutan. Dis., 44:1, 1906.
5. Joisten, Erich: Zwei Ätiologisch Unklare Falle von Gangränescierender Entzundung der Nase und des Oberkiefers. Ztschr. f. Hals- Nasen- und Ohrenheilkunde. 41:105 (Sept. 16) 1936.
6. Jones, H. M.: Esthiomenic Menstrual Ulcer of the Nose. Jour. Laryngol. and Otol., 12:301, 1897.
7. Lewy, Alfred: A Case of Gangrenous Osteomyelitis of the Paranasal Sinuses. Arch. Otolaryngol., 27:91, 1938.
8. McArthur, G. A. D., and Dew, H. R.: Case of Malignant Granuloma of the Nose. Jour. Laryngol. and Otol., 40:378 (June) 1925.
9. McBride, Peter: Case of Rapid Destruction of the Nose and Face. Jour. Laryngol. and Otol., 12:64, 1897.
10. Nabarro, David: An Obscure Case of Ulceration of the Nose in a Child Simulating an Epithelioma. Brit. Jour. Surg., 1:576, 1914.
11. Schütz, Walter: Verschiedene Formen von Gangrän der Nase und Nasennebenhöhlen. Ztschr. f. Hals- Nasen- und Ohrenheilkunde, 44:244 (Nov.) 1938.
12. Stewart, J. P.: Progressive Lethal Granulomatous Ulceration of the Nose. Jour. Laryngol. and Otol., 48:657 (Oct.) 1933.
13. Wood, G. B.: A Case of Mutilating Granuloma of the Nose and Face with Fatal Ending. Trans. Am. Laryngol. Assn., 1931, p. 63.
14. Woods, Robert: Malignant Granuloma of the Nose. Brit. Med Jour., 2:65 (July 16) 1921.
15. Wegener, F.: Uber eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung des Arterien-Systems und der Nieren. Beitr. z. path. Anat. u.z. Allgem. Path., 102:36 (Jan. 5) 1939.

DISCUSSION

J. C. BECK, M.D., Chicago: I do not believe I should add, or can add, anything to the paper that has just been presented. I have been very much pleased to receive a copy of this paper, and I have gone over it.

The only thing I can say concerns the one case of a patient of Doctor Levy, of Chicago. I had the opportunity of following this case in consultation at our infirmary. It presented a condition of chronic granulomatosis, of which there are a number. It was practically the same as the cases which have been quoted here, and aside from the fact that the newer chemotherapy measures seem to indicate something along the therapeutic line, we must still believe definitely that the etiologic factor, as Doctor Hoover said, is one thing that we must find.

It seems that through the chemotherapy of the newer types, we are going to be led in the direction of the etiology.

WALTER B. HOOVER, M.D., Boston: I have practically nothing more to say about this subject. I wrote down all I know about it in the paper, and anyone wanting to get more details will have to read that.

It is a subject that is extremely interesting to me. When I saw the second case, which was so similar to the cases which went on to death, I thought surely I should be bold enough to ask permission to present this subject before the Academy, because I am sure that many similar cases will be seen by members of this body.

SURGICAL TREATMENT OF BILATERAL PARALYSIS OF THE ABDUCTOR MUSCLES OF THE LARYNX

JOSEPH D. KELLY, M.D.
NEW YORK

IT IS the purpose of this paper not to discuss at length the symptoms, diagnosis, and causes of bilateral paralysis of the abductor muscles of the larynx, but to cover in a general way the surgical treatment and the results obtained by the various operations. In other words, it is an attempt to answer the questions, "What can I do to relieve the patient suffering with bilateral paralysis of the abductor muscles, and what results can I expect?"

In October, 1939, I saw a patient in one of the public hospitals in New York City who was suffering from this condition which had followed several operations on her thyroid gland. She wanted to have something done to relieve her of the tracheotomy tube, and she wanted it to be done quickly because of the annoyance caused by the tube in her trachea. I assured her that something would be done at the first opportunity. Up to this time, my one and only resection of the cord had been a failure, and, on consulting the literature, I found that there had been few successful operations performed and reported. Either the patient had an adequate airway sufficient for his normal requirements and the voice was very poor, or the voice remained good and the patient could not be decannulated. After study I concluded that the problem of bilateral paralysis of the abductor muscles might be considered in the following manner:

Bilateral abductor paralysis is of two types:

1. That which comes on gradually as a result of injury to the recurrent nerves and that which comes on as a result of lesions or infections of the central nervous system, which may be borne by the patient without his succumbing to tracheotomy.

2. That which is ushered in with a violent spasm of the conus muscularis of the larynx, causing a most distressing dyspnea and relieved only by a tracheotomy.

Patients with the first type, even though they are incapacitated and suffer much distress from dyspnea, abhor the idea of a tracheotomy. Those with paralysis of the second type, although they welcome the tracheotomy as a life-saving measure, soon tire of the tracheotomy tube which deprives them of their voice and irritates their trachea. Even though the laryngologist is able to supply them with the ingenious Tucker tube or some other by-valve tube to strengthen their voice, they will ask to be relieved of the annoying cough and tracheal reflexes caused by the tracheotomy tube. Hence, all of these patients look for an operation which will restore the larynx as a breathing tube and will preserve a pleasant, useful voice.

To this end several groups of operative procedures have been devised. Of the first group, perhaps the ideal operations were those which attempted to suture the ends[2] of the severed nerve or to anastomose it with one of the nerves in the neck. These operations were not successful because the ideal is difficult to obtain and because it was found that the impulses arriving as a result of suture or

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

anastomosis were transmitted not only to the abductor muscles but also to the adductor muscles, producing spasmodic movements of the cords, and left the patient as distressed as he was before the operation. Also, the operations had a very limited use, because they could be carried out only in those cases in which the surgeon was positive that the nerves had been cut and that he could pick up one or more severed ends. Ballance, Frazier, and Lahey were the pioneers who attempted to accomplish this ideal.

Operations of the second group were directed at the interior of the larynx and at the paralyzed cords themselves. It seemed a logical thing that if the surgeon could eliminate one cord the patient would have more breathing space; and with the other cord in the midline, there was hope that he would have a satisfactory voice. Hence, the development of cordectomy. This operation was tried and was found a failure, because scar tissue readily formed a new cord and often caused more distress to the patient than he had suffered before the operation. Some laryngologists[4] at this time felt that the removal of more tissue would bring the cicatrices closer to the internal surface of the thyroid cartilage, thus leaving a larger aperture in the larynx. It was thought that if the ventricle and the cord were removed at the same time, the operation would be a success. However, this procedure failed too. Scar tissue formed and in some instances cicatricial stenosis developed. It had many weaknesses, it was inaccurate, and it neglected any consideration of the voice-producing tissues of the larynx. It was not a satisfactory surgical procedure.

Doctor Hoover[3] realized that the failure of all these procedures was due to intralaryngeal scar tissue formation, and he tried to overcome this by doing a submucous resection of the cord and adjacent tissues following laryngofissure. This operation was a step in the right direction. This procedure has proved successful in the hands of Doctor Hoover, but it has been a failure in those of many others, including my own. I can but praise the operation; it was with this method that laryngologists had their first success. I find that Doctor Hoover[7] has reported satisfactory conclusions in 75 per cent of the cases in which he has operated but has admitted that the patients have a poor voice. A few other surgeons also have reported good results with this technic; however, the submucous resection is difficult,[12] and I believe that it was with the idea of simplifying this part of the Hoover operation that Doctor Loré,[8] of New York City, came forward with his method of elevating the mucous membrane over the area in which Hoover did a submucous resection. By elevating the mucous membrane, it was possible to come down directly on the tissue to be removed; hemorrhage was more readily controlled, and a more complete removal of the tissue could be made under direct vision. Loré went a step farther in his proposed operation, and instead of just removing a part of the vocal process of the arytenoid, he removed it completely. This part of his procedure, I believe, spelled success for his method, because the greatest number of favorable results for the relief of abductor paralysis has been obtained by operations which involved the arytenoid cartilage. However, Loré was not the first surgeon to think of the removal of the arytenoid cartilage as a help in relieving this condition. Dr. Charles H. Baker,[1] of Bay City, Michigan, reported the case of a nine year old boy upon whom he operated in 1916, removing the right cord and arytenoid cartilage following laryngofissure, with an excellent result. In view of the result obtained by this physician and recorded in his published paper, it seems that laryngologists neglected something by waiting

CHART I.

Ventriculocordectomy—The Results Obtained by Various Operations.

SURGEON	NUMBER OF CASES	RESULTS		COMPLICATIONS	COMMENTS
		Voice	Air-way		
Figi	1	Not stated.	Inadequate.	None.	None.
Hitz	1	Worse.	Inadequate.	None.	"Tried operation twice."
Stokes	9	Worse 2 Unimproved 7	Inadequate 9	Hemorrhage ? Synechia ? Mediastinitis 1.	"Operation unsatisfactory."
Clerf	5	Worse 5.	Inadequate 5.	None.	"In none of these were the results satisfactory, for the voice was seriously impaired; in addition, there was ultimate return of much of dyspnea due to cicatricial changes."

Cordectomy—The Results Obtained by Various Operations.

SURGEON	NUMBER OF CASES	RESULTS		COMPLICATIONS	COMMENTS
		Voice	Air-way		
Birkett	1	Worse.	Inadequate.	None.	"No improvement."
Howell	1	Improved.	Inadequate.	None.	"Not a success."

CHART II.

Submucous Resection of Cord and Vocal Process of Arytenoid—Hoover Technique.

SURGEON	NUMBER OF CASES	RESULTS		COMPLICATIONS	COMMENTS
		Voice	Air-way		
Stevenson	1	Improved.	Adequate.	Hemorrhage.	"Satisfactory breathing."
Kistner	2	Unimproved.	Adequate.	None.	None.
Tobey	1	Unimproved.	Adequate.	None.	"Submucous of the cord and fixation to thyroid cartilage with catgut."
Beyer	1	Improved.	Inadequate.	None.	"This patient was not decannulated because he lived in the country."
Hoover	8	Worse 8.	Adequate 6. Inadequate 2.	Infection 1. Unknown 7.	"The operation sacrifices the voice in a large measure. We feel that the 75% excellent results can still be further improved."
Stokes	4	Unimproved.	Not stated.	Not stated.	"In my own small personal series (13 cases) I favor the laryngofissure with unilateral complete excision of vocal cord, ventricular band and vocal process."

until 1932 for Doctor Hoover to start them thinking again. The only reason for delay in accepting Doctor Baker's technic is that they were afraid of removing too much tissue from the larynx, which would be tragic, and the fact that his was the only case reported up to that time.

the operation. Such was the status of Doctor King's[5] operation when I was trying to find some sound method for handling the case of double abductor paralysis on my service. However, the operation appealed to me because: first, it was extralaryngeal and thereby the formation of scar tissue could be avoid-

CHART III.

Submucous Resection of Cord and Arytenoid Through Laryngofissure—Lore Technique.

SURGEON	NUMBER OF CASES	RESULTS		COMPLICATIONS	COMMENTS
		Voice	Air-way		
Rawlins	1	Worse.	Adequate.	None.	"Perfect result except for voice. Only necessary to operate on one side to get good result."
Johnson	1	Improved.	Adequate.	None.	"Voice is better than in those who have had King operation done. Also, removal of arytenoid is most important step."
Baker	1	Good.	Adequate.	None.	Operationwas performed in 1916.
Woodward	1	Worse.	Inadequate.	None.	"A very unsatisfactory procedure. Operation was carefully and completely done."

In 1939, Dr. Brien T. King,[5,6] of Seattle, who is a general surgeon and trained in orthopedics, suggested that the solution for this problem was practically the same as that for paralytic ankylosis of any other joint in the body. He insisted that there was no need for intralaryngeal surgery. He proposed substituting viable muscle for paralyzed muscle, and in these cases he attached the anterior belly of the omohyoid muscle to the muscular process of the arytenoid cartilage. Successful results were achieved and were later reported. This procedure certainly appealed to every laryngologist confronted with a case of abductor paralysis. Operations of this type were performed by enthusiastic laryngologists, but the successes reported were few. The value of the method began to be doubted when improvement did not take place two or three months following

ed; second, it preserved the tissue of the larynx thus increasing the chances of the patient having a good voice; third, it was directed toward the arytenoid cartilage which was important to me at the time. However, I could not see the virtue of trying to attach the omohyoid to the arytenoid cartilage, because I felt that the best one could expect would be that the muscle would attach itself to the surrounding tissues and not to the cartilage. I felt that if the arytenoid cartilage were removed by an extralaryngeal route, the result should be good. Since reporting his first case, Doctor King[6] has improved his technic by the simple expedient of completely mobilizing the arytenoid; he cuts it practically free from the articular process of the cricoid cartilage. Doctor King tells his own story in the way of a personal communication in answer to one of my questionnaires, dated July 31, 1940.

I have now operated upon 24 patients for bilateral abductor cord paralysis, of whom 22 were females and 2 were males. The ages varied from 26 to 73. There have been no deaths. The complications were as follows: Six infections; one case of chronic tetany (the patient gave a history of chronic tetany at the time of operation for goiter). Twenty-two patients had had thyroidectomy, and two of these developed infection of the larynx; one was a tuberculous infection and the other probably streptococcal, the latter occurring in a child one and a half years old.

The operative procedure consisted of a simple transposition of the omohyoid muscle in three instances. In 21 cases the operation consisted of a thorough division of the cricoarytenoid joint capsule and outward displacement of the cartilage. In 23 cases the omohyoid muscle was transposed, and in one case it was not. (In the latter case an excellent airway resulted and a fairly good voice was restored. The patient gained 32 pounds. Paralysis had been present for 18 years). In two cases the lower half of the arytenoid cartilage was removed, although this had not been planned as a part of the operative porcedure. The cartilage was fractured in attempting to pass a suture through it, and the lower half was so separated from the surrounding structures that removal was essential because no circulation could possibly have been left to supply it. In these cases the patients secured good results both from the standpoint of airway and voice. However, the airways were not as ample as those in a number of the other patients who had been operated upon in this series. In other words, the outward displacement of the vocal cord was not as great as it was when the cord was pulled outward by displacing the arytenoid cartilage outward.

I do not doubt that all of these patients would have obtained as good results with outward displacement of the arytenoid cartilage as with displacement and transposition of the omohyoid muscle. When my original article was published, I attached more importance to transposition of the muscle than I do at the present time, and perhaps I will discontinue the procedure of transposing the omohyoid. Special attention to the larynges of these patients is important during operation to determine whether sufficient airway is obtained.

CHART IV.

King Operation—And Results Obtained by Various Operators.

SURGEON	NUMBER OF CASES	RESULTS		COMPLICATIONS	COMMENTS
		Voice	Air-way		
Figi	1	Not stated.	Inadequate.	None.	"Patient able to breathe freely with cannula corked 2½ months following operation, but has not yet been decannulated."
Knight	1	Unimproved.	Inadequate.	None.	"About 30% improvement in abduction of right cord, not sufficient for decannulation."
Rives	1	Unimproved.	Inadequate.	None.	"Operation failed because muscles and facia of intra-arytenoid structures were not severed. There was motion of left arytenoid following operation."
Clerf	3	Normal 3.	Inadequate.	Skin Infection 1.	"In two cases, there was motility and increase in the air-way so that patient could wear the cannula blocked. In the third case, one month after operation, there is no motion of larynx and patient has not been decannulated."
King	24	Good 22 Poor 2.	Adequate 24.	Infection 6	"Three cases had simple transposition of omohyoid muscle. Twenty-one cases had complete division of cricoarytenoid capsule and outward displacement of the arytenoid cartilage."

From this communication it will be observed that Doctor King began to get his greatest number of successful results when he completely mobilized and displaced outward the arytenoid cartilage, that he is now of the opinion that transplantation of the omohyoid is not necessary to the success of his operation, and that in the future he will most likely confine his efforts to the arytenoid cartilage.

Reverting to the case on my service, which was mentioned here previously, something had to be done to satisfy and relieve the patient, and I could not readily decide which type of operation would offer definite satisfactory results. Of prime importance was the fact that this patient would not submit to a surgical procedure if there were a possibility of her being deprived of her voice. To make certain that this would not result, a surgical procedure as extralaryngeal as possible would be necessary. If that were carried out, the possibility of intralaryngeal contractions conducive to voice impairment would not be so great. I concluded that if an arytenoidectomy were performed through the wing of the thyroid cartilage, three things might be accomplished.

1. The tension of the cord on that side, caused by the action of the cricothyroid muscle would be eliminated, and the cord would fall away from the midline of the larynx.

2. The space created by removal of the arytenoid cartilage would be obliterated by nature and would thereby cause an atrophy of the muscles on that side. This would enlarge the area between the cords posteriorly.

3. The position of the anterior third of the cord would be slightly altered in relation to the unoperated side, and the proximity of the cords would be preserved to a reasonable extent. As a result, the patient's voice would be maintained.

With these ideas in mind, my associate, Doctor John F. Daly, and I proceeded to practice on cadavers in an effort to determine the feasibility of extracting the arytenoid cartilage. In examining the larynx, we found that if a window were made in the lower posterior third of the thyroid cartilage limiting its anterior border by a line and separating the middle and the posterior inferior third of the thyroid cartilage, we would come down upon the muscle structure covering the arytenoid cartilage, and by careful dissection, the arytenoid cartilage could be removed with little damage to the intralaryngeal mucous membrane. We also noted in examining the larynx after carrying out this procedure that the cord on the operated side fell away from the median line and assumed a lower level than the cord on the unoperated side; and if nature followed her usual course in repairing tissue by obliterating cavities, the contraction of the cavity left by the removal of the arytenoid cartilage would give the patient a satisfactory airway.

We were undecided about the method to be used to anesthetize our patient. The tracheotomy tube could not be removed for more than half a minute because of the peculiar conformation of scar tissue in the skin surrounding the tracheotomy opening. When the tube was removed, the scar tissue contracted, and the patient was unable to inspire air through the opening. She was also unable to inspire through the larynx because the cords were overlapping. There were contractions of the old thyroidectomy scars which prevented the patient from lifting her chin. When she did raise her chin, the tracheotomy opening became tighter as a result of the tension on the scar tissue. Therefore, it was decided that the operation be performed under general anesthesia so that if any unforseen eventualities should occur, they could be handled quietly and de-

liberately. Together with Doctor Paluel Flagg, our anesthetist, we worked out a plan to give the patient some preoperative sedation and to start the anesthesia through the tracheotomy tube. When the patient became sufficiently anesthetized, Doctor Flagg was to endeavor to pass an intratracheal tube through the cords into the trachea. The tracheotomy tube could then be removed, and the patient would be in an ideal condition for the operation. The above procedure was carried out, and the patient's condition remained satisfactory. The scar tissue of the neck which caused contracture from the posterior surface of the arytenoid cartilage for which adrenalin and pressure were used to control the bleeding. Otherwise, the procedure was uneventful. The skin of the neck was closed, and a stab wound was made in the skin (Fig. 2) over the thyroid cartilage into which a cigarette drain was placed and left in position for five days. A stomach tube was inserted through the patient's nose and was left in position for five days. The tracheotomy tube was put back in place, and after a week or ten days the patient began to breath through her larynx.

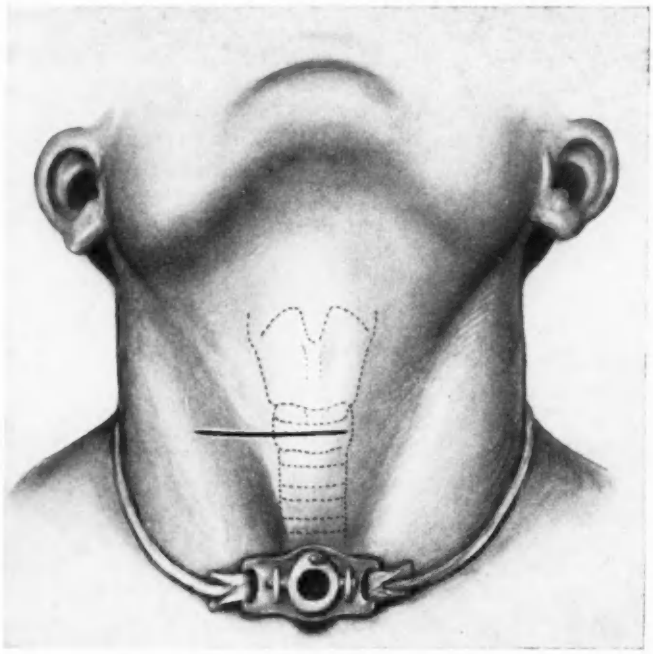


FIG. 1 — Location of incision in second operation.

was cut away, and the larynx was exposed on the left side. A window was made at the selected position in the thyroid cartilage, and dissection was done in the same manner as that on the cadaver (Fig. 1). A small artery was cut in dissecting the muscle tissue away

The operation was performed on November 3, 1939, and the patient was discharged from the hospital on November 15, at which time she was wearing a stopper in her tracheotomy tube continuously. Improvement in the condition of the patient's larynx was noted from

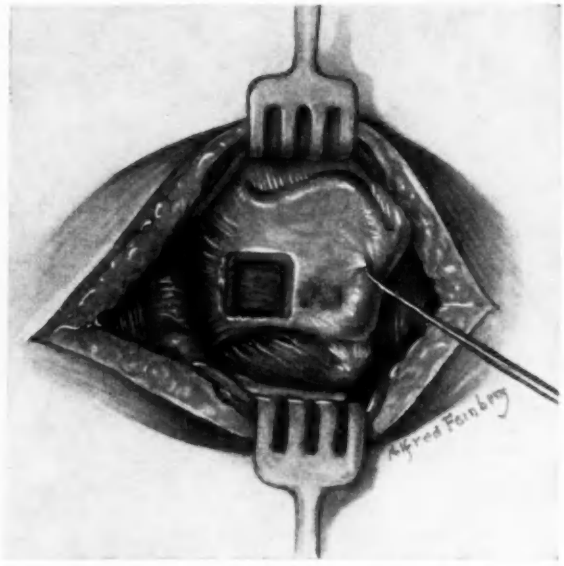


FIG. 2 — Exposure of muscle tissue over arytenoid cartilage.

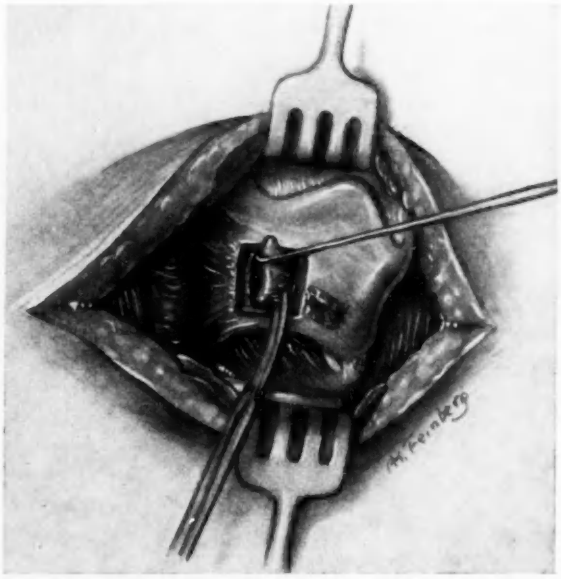


FIG. 3 — Dissection of arytenoid cartilage through muscle tissue.

November 15 until she returned to the hospital on January 4 for removal of the tube. This was done the day she entered the hospital. She was dismissed from the hospital six days later at which time she was able to do without the cannula. The patient has since carried on her duties as a housewife with little inconvenience.

Since performing the first operation, I have felt that this procedure could be done under local anesthesia with safety and with very little discomfort to the patient. We did perform this operation under local anesthesia on February 19, this year. The case was referred to us by our Bronchoscopic Department. The patient was a man 68 years old, who had been affected with bilateral abductor paralysis for which he had been wearing a tracheotomy tube for almost a year. He was very anxious to obtain relief from severe coughing spells and irritation which occurred when he retired. He felt that the tracheotomy tube was causing his spasms, because when it was removed, he obtained definite relief.

A local anesthetic was used in this case. We noticed in performing this operation that it was more difficult to remove the arytenoid than it had been in the first case. This I believe to be due to the fact that in the first operation, where a general anesthetic was given by intratracheal tube, the intratracheal tube helped to fix the arytenoid in one position and the tube acted as a point of counter pressure in cutting the arytenoid free from the articular surface of the cricoid. In the future, I shall have a bronchoscope passed before performing the operation under local anesthesia. We used a half Kocher incision in this case for exposing the right side of the larynx. The incision made by Doctor King is very serviceable and does not require cutting any pretracheal muscles, but I believe that the half Kocher incision leaves a better scar.

FIG. 4 — Position of right cord two months after operation.

It was remarkable to see the slight interference with deglutition which was caused by removal of the arytenoid cartilage under local anesthesia in this case. After we had finished the operation, the patient sat up on the table and asked for a drink of water. He drank without any evidence of difficulty or distress. Because of this, he was permitted to remain on a full, unrestricted diet during the period of his convalescence.

Incidentally, this patient was affected with advanced cardiorenal disease. His blood pressure registered two hundred and over during his stay in the hospital. He was decannulated five weeks after the operation and was permitted to return home. After remaining home for about a week, he was returned to the hospital because he was having difficulty in breathing. Examination of the larynx revealed that the airway was ample, in fact it was more so than that of the patient upon whom we had operated a year previously. The patient was very nervous. His pulse was rapid, and his blood pressure registered over 220. A quarter grain of morphine was administered hypodermatically following which the patient quieted down until midnight when

CHART V.

Compilation of Results Obtained by Various Operative Procedures.

OPERATIONS	NUMBER OF CASES	ETIOLOG	TRACHEOTOMY DONE IN	RESULTS		FAILURES
				Voice	Air-way	
Ventriculo-cordectomy	16	Thyroidectomy 14. Tumor of Neck 1. Syphilis 1.	16	Poor 16.	Adequate 0	16
Cordectomy Intra-oral	2	Thyroidectomy 2.	2	Improved 1. Worse 1.	Adequate 0	2
Submucous Cordectomy (Hoover)	17	Thyroidectomy 16. Diphtheria 1.	Unknown.	Improved 2. Unimproved 15.	Adequate 10. Not Stated 4. Inadequate 3.	3
Submucous Cordectomy and Arytenoidectomy (Lore)	4	Thyroidectomy 2. Diphtheria 2.	2	Improved 2. Worse 2.	Adequate 3.	1
King Operation	30	Thyroidectomy 28. Infection 2.	Unknown.	Improved 27. Poor 3.	Adequate 24.	6
Arytenoidectomy Extra-laryngeal	2	Thyroidectomy 1. Central Lesion 1.	2	Improved 2.	Adequate 1.	1

It will be noted on this chart that the greatest number of successes were obtained in those operations which prevented the formation of scar tissue, and either removed the arytenoid cartilage or completely mobilized it so that it could be fixed in abduction.

morphine again was required. The following day the tracheotomy wound was reopened, and a tube was inserted. During the remaining five days while the patient was in the hospital, the tube was kept corked. A week or so after leaving the hospital, he expired as a result of cardiac thrombosis.

When Doctor Myers asked me if I would read a paper on this subject at the meeting of the Academy, I gladly consented. I had three reasons for doing so. First, I believed that the literature on the subject of surgical treatment of bilatreal abductor paralysis was confusing (however, this was before Doctor King's report on his twenty-four cases). Second, I felt that I might be able to render a service to the Academy if I could get opinions from others with regard to their experiences with this type of case and whether or not they had followed any surgical procedures other than tracheotomy. I felt that if this data were compiled and tabulated, we would have some knowledge of what had been accomplished in this field. From this tabulation we might develop a plan to follow in the treatment of those cases of bilateral abductor paralysis which come under our care. Third, I wished to report these two cases for your consideration.

To obtain this data, I sent out one thousand questionnaires to the members of the various National societies, and from these I received one hundred and twenty-one replies. Many of those who replied were most anxious to help by giving whatever information they had, and I wish to take this opportunity to thank them. A set of charts has been compiled which may be of interest and which substantiates some of the statements and conclusions made in this paper.

SUMMARY AND CONCLUSIONS

It is my belief that not all patients with bilateral paralysis of the abductor muscles need immediate operation. A patient, whatever the cause of his paralysis, with the cords in the cadavaric position, with a good voice, and with no dyspnea on ordinary exertion may be watched until he seeks relief. Such a patient in confinement or under circumstances requiring excessive physical strain should be tracheotomized and operated on for paralysis of the abductor muscles at his convenience and that of the physician. From my study and experience, I believe it is wise to wait from six months to one year before operating unless it is definitely known that the nerves have been cut, because there have been reports of restoration of function after an elapse of eighteen months.

I feel that the surgical data gathered through questionnaires proves without doubt that the greatest success in the surgical treatment of bilateral abductor paralysis is attained by those operations which attach the arytenoid cartilage either extralaryngeally or intralaryngeally. In view of the number of successful cases reported by Doctor King, it seems imperative that we should try the King operation before any other extralaryngeal procedure. Arytenoidectomy, either through the King incision or through the wing of the thyroid cartilage, should be tried on one or both sides before resorting to an intralaryngeal operation. If the external operation on the arytenoid fails, intralaryngeal surgery is in order, and I prefer the resection of the thyroarytenoideus and the cricoarytenoideus lateralis muscles after the method of Loré or Rawlins.[9,11]

If we follow this sequence in the surgical treatment of bilateral abductor paralysis, we will most thoroughly conserve the interests of the patient.

REFERENCES

1. Baker, C. H.: Report of a Case of Abductor Paralysis with Removal of One Vocal Cord, J. Mich. M. Soc. 15:485 (Oct.) 1916.
2. Frazier, C. H., and Mosser, W. B.: Treatment of Recurrent Laryngeal Nerve Paralysis by Nerve Anastomosis, Surg., Gynec., and Obst. 43:134 (Aug.) 1926.
3. Hoover, W. B.: Bilateral Abductor Paralysis; Operative Treatment by Submucous Resection of the Vocal Cords, Arch. Otolaryngol. 15:339 (Mar.) 1932.
4. Jackson, Chevalier: Ventriculocordectomy, a New Operation for Cure of Goitrous Paralytic Laryngeal Stenosis, Arch. Surg. 4:257 (Mar.) 1922.
5. King, Brien T.: A New and Function-Restoring Operation for Bilateral Abductor Cord Paralysis; Preliminary Report, J.A.M.A. 112:814 (Mar. 4) 1939.
6. King, Brien T.: A New and Function-Restoring Operation for Bilateral Abductor Cord Paralysis, Tr. Am. Laryng. Assoc. 60:264, 1939.
7. Lahey, Frank, and Hoover, W. B.: Injury to Recurrent Laryngeal Nerve in Thyroid Operations; Their Management and Avoidance, Am. Surg. 108:545 (Oct.) 1938.
8. Loré, John M.: Suggested Operative Procedure for the Relief of Stenosis in Double Abductor Paralysis; Anatomic Study, Ann. Otol., Rhin., and Laryng. 45:679 (Sept.) 1936.
9. Rawlins, A. G.: Operative Procedure for the Relief of Stenosis in Double Abductor Paralysis of the Larynx, Laryngoscope 49:260 (April) 1939.
10. Rethi, Aurel: The Treatment of Laryngeal Stenosis Caused by Bilateral Abductor Paralysis, Tr. International Congress of Otol., Rhin., and Laryng., Cophenhagen, 1928.
11. Stevenson, W.: Submucous Cordectomy for Bilateral Abductor Paralysis; Report of a Case, Ann. Otol., Rhin., and Laryng. 46:531 (June) 1937.
12. Zinn, W. F.: Postoperative Bilateral Abductor Paralysis, Ann. Otol., Rhin., and Laryng. 44:164 (Mar.) 1935.

DISCUSSION

M. C. Myerson, M.D., New York: For many years we have been looking for the solution to the problem presented by bilateral abductor paralysis. It is briefly this: How can we provide a laryngeal airspace adequate to maintain a normally functioning individual

without sacrificing his voice? Doctor Kelly is the latest of a long line of earnest workers who have tried to solve this problem. Jackson, Hoover, Rethi. Loré, Rawlins, King, and others have suggested and performed various operations, some of which proved of value. The ventricolocordectomy of Jackson has been abandoned; the operations of Hoover, Rethi, Loré, and Rawlins, though furnishing adequate airway, have not fulfilled the requirement of a good voice. Following King's operation a good voice is retained, and apparently the individual is able to maintain his normal activities.

Doctor Kelly's operation does not disturb the voice; it adds a millimeter or more to the glottic space. This, to my mind, is sufficient to maintain an individual who is not too active, but cannot be relied upon for excitable and active patients. I performed the Kelly operation for removal of the arytenoid on one of my patients. Following the procedure the vocal cord on the operated side took a lower and more lateral position. As a result of the operation, the patient can go for many days and nights with her tracheal cannula corked. Unfortunately, however, she becomes severely dyspnoeic on exertion or during excitement. For this reason she has not been decannulated.

This patient, as others who try to carry on with a narrowed airway, suffers a considerable degree of oxygen want. I wish to emphasize this. We all have seen patients, who have been tracheotomized following an accident or following a streptococcic or leutic infection, in whom the airways are not sufficiently adequate to enable them to function as normal individuals. They get along quite well, but they present a definite picture of anoxemia. They have bulging eyeballs, are pallid, have palpitation on exertion, have an increased pulse rate, and cannot engage in activities that the average normal individual of their age group does. Anoxemia must be reckoned as an important factor in decisions for or against decannulation.

Doctor Kelly is to be congratulated upon his idea and its fine execution. Work such as this should be encouraged, for it is only by the efforts of many that best results are obtained.

I have corresponded with Doctor King ever since he first published an account of his work, and I felt, as a result of my own experience with three cases, that perhaps we were not performing this operation in the same manner that he does. I know that I did not.

In two of my cases, I was so impressed by the omohyoid implant that I disregarded the step of pulling the arytenoid laterally. As a result, I had failures. In the third case, I pulled the arytenoid laterally, but had trouble passing my suture. At first, I tried to pass the needle through the arytenoid, and finally decided to pass the suture around the cartilage and through the perichondrium, but had much trouble and lost a good deal of time. I believe this difficulty accounted for the infection that ensued and which nullifiied my possible good results.

In a letter received from Doctor King yesterday morning, he states that three patients upon whom he has performed this operation are quite active at the present time. One is a man who is in the hardware business, another is a trouble-shooter for a telephone company, and the third is one of the secretaries of a very active physician in Chicago.

I telephoned this secretary yesterday morning. I was astonished at her very fine voice and at the story she told. She said that she could dance, could run upstairs, and in fact was able to do anything that anybody of her age could do, without distress from dyspnea.

So, for the present I believe that the best procedure we have thus far is the King operation.

WALTER B. HOOVER, M.D., Boston: I wish to compliment Doctor Kelly and to express my gratitude to him for this fine presentation. This subject has been a hobby of mine for the past twelve years, and I feel that the solution is still not 100 per cent. I do not believe that it ever will be.

To date, I think that it has not been possible to restore normal function to a larynx affected with bilateral abductor paralysis due to section of both recurrent laryngeal nerves. I see no possible way for the vocal cords to be separated sufficiently for active respiration and yet be brought together with good tension for a perfect voice. In order to have a normal voice it is necessary to have good tension of normal vocal cords with good approximation of them, and in order to have adequate respiratory function the cords must be separated. When these two functions are perfect, there is normal collaboration, which is the status of the larynx before injury occurs to the laryngeal nerves.

Primarily, of vital concern is maintaining the natural function of the vocal cords. Therefore, I feel that every one of us is obligated to stress to the general surgeons the need for careful laryngeal examinations and preservation of the laryngeal nerves during thyroid operations. Certainly, prevention of paralysis is of supreme importance.

I believe that tracheotomy with the Tucker valve is effective and should be used in a large percentage of these cases, because many patients are satisfied with a tracheotomy tube. A patient of mine said that she would rather have a tracheotomy tube than wear her false teeth. But all people are not like that. There are others who would rather die than have a tracheotomy tube, and I know a patient who did die rather than have one.

I have now performed the submucous operation in twelve cases out of about fifty affected with bilateral abductor paralysis. I have corrected the two failures, which were shown on the board, by a second operation this past summer. The reason why the failures occurred was because infection developed. One of these patients had a severe sinusitis. Treatment for the sinusitis was given, and the second operation has brought about satisfactory results. The other patient developed an infection following a vomiting spell during the course of the operation under local anesthesia.

The submucous operation I believe can be done more readily under general anesthesia, and I feel that intravenous pentothal is the anesthesia of choice. It should be supplemented by local anesthesia, and oxygen should be administered through the tracheotomy tube. I would advise that a tracheotomy tube be inserted before the operation is begun because some swelling may develop following surgery. This precautionary measure for the maintenance of adequate breathing in case of emergency is invaluable and may mean the preservation of a patient's life.

I believe that following the operation, a tube for feeding is advantageous. It may not be necessary, but it has definite benefits. When it is used, the results can be ascertained with more of a degree of certainty than otherwise.

I wish to thank Doctor Kelly for his presentation, and because the time allotted for this discussion is limited, I shall not comment further.

JOSEPH D. KELLY, M.D., New York: I wish to thank Doctor Myerson and Doctor Hoover for discussing my paper. I agree with Doctor Myerson that this is not a completely satisfactory operation for the relief of bilateral abductor paralysis. In fact, I do not believe that there is an operation for this condition at the present time which is completely satisfactory. However, I do think that every improvement which is made should be encouraged. I wanted to present this type of procedure which has been successful in decannulating two patients.

(Slide.) This is the incision which I use. It is made just above the cricoid cartilage. The pretracheal muscles are incised and are lifted out of the way for the exposure of the thyroid cartilage.

(Slide.) Here, exposure of the thyroid cartilage is shown. In making our investigation, we found that the vocal cords were about on the same level as the thyroid notch. A window was made at the junction of the posterior and middle third of a line drawn from the thyroid notch to the posterior border of the thyroid cartilage on the side to be operated.

(Slide.) Removal of the arytenoid cartilage through the window is carried out. The instruments used in holding the arytenoid cartilage are small single and double hooks, which were devised for this procedure. After the arytenoid is removed, the incision on the neck may be closed and a cigarette drain left in place over the larynx. The two patients upon whom I did this operation have made uneventful recoveries, the drain being removed on the fifth day.

Some features of this operative technic, some of Doctor King's, and some of Doctor Hoover's may later be helpful in devising a technic which will be entirely satisfactory for the relief of this condition.

I agree with Doctor Hoover that some patients are content with their tracheotomy tubes, but they usually are patients who do not have to work for a living and who have a good mental balance. However, the patient who needs to be employed desires to be rid of the tube. Very often the presence of a tracheotomy tube, in these days of severe competition, is an unsurmountable handicap to the patient seeking employment.

SUSPENSION LARYNGOSCOPY IN THE TREATMENT OF MALIGNANT DISEASE OF THE HYPOPHARYNX AND LARYNX

GORDON B. NEW, M.D.*

and

HOWARD E. DORTON, M.D.†

BY INVITATION

ROCHESTER, MINNESOTA

DURING the eleven year period, 1927 to 1937 inclusive, a selected group of thirty-eight patients with malignant disease of the hypopharynx and larynx have been treated at the Mayo Clinic with the aid of suspension laryngoscopy. Surgical diathermy and radium emanation seeds have been employed, and, in addition, external irradiation has been used at times.

While suspension laryngoscopy has been used for many years, its value in the treatment of malignant diseases of the hypopharynx and larynx is not generally known. We feel that carefully selected patients can be taken care of with less surgical risk when laryngeal suspension is employed. Immediate histologic diagnosis by the fresh frozen section is an essential part of this method.

Lynch[3] did more than anyone else in this country to perfect and stimulate interest in suspension laryngoscopy. In 1928, he reported dissection with a knife of early intrinsic laryngeal epithelioma under suspension and recommended its use in certain selected cases.

Killian,[1] in giving the Semon lecture, stated that Mayer removed an epithelioma of the epiglottis in 1914 under suspension laryngoscopy but said that such cases ought to be selected with care.

At the Mayo Clinic we have used suspension laryngoscopy for many years and feel that it has a definite place in the treatment of cancer of the hypopharynx and larynx. However, the apparent lack of widespread knowledge of its usefulness is shown by a statement of Thompson[4] in 1939 when he said, "Operation per vias naturales is now only of historical interest, though pathologically of some importance," and he attributed the occasional rare instances of cure by this route to low grade lesions of minor extent.

SELECTION OF CASES FOR TREATMENT

Our series consists of thirty-eight cases of malignant disease in the hypopharynx and larynx in which treatment was given under suspension laryngoscopy during the years 1927 to 1937 inclusive. During this same period approximately 450 patients were operated on at the clinic for malignant disease of the larynx and hypopharynx. This brings out the fact that the cases in which treatment was given under suspension laryngoscopy are a selected group.

We have divided the cases into five groups depending on the location of the growth: (1) growths at the base of the tongue in the hypopharynx; (2) supraglottic growths; (3) intralaryngeal growths; (4) growths involving the lat-

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

* Section on Laryngology, Oral and Plastic Surgery, Mayo Clinic, Rochester, Minnesota.

† Fellow in Surgery, Mayo Foundation, Rochester, Minnesota.

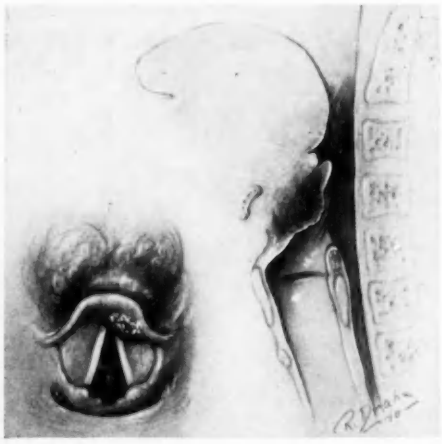


FIG. 1 — A man, aged fifty-five years, with squamous cell epithelioma grade 4 on the posterior surface of the epiglottis extending down into the larynx and producing edema at the base of the tongue. Preliminary tracheotomy was made, the epiglottis and growth were removed with diathermy, and emanation seeds were inserted into the base. Further radium seeds were inserted into the base of the tongue and epiglottis with no evidence of recurrence for two years.

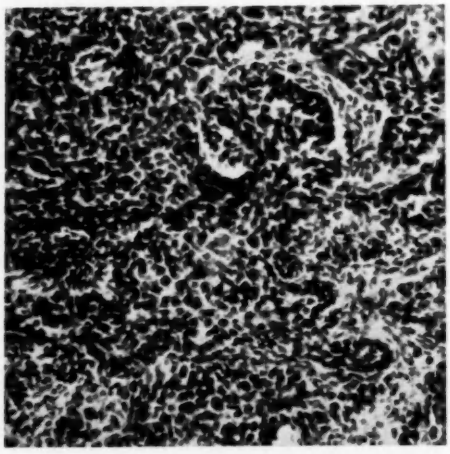


FIG. 2 — Same case as figure 1 (×200).

eral and posterior walls of the hypopharynx, and (5) postcricoid growths. Some of these lesions involved two or more of these sites, but we grouped them according to the place where the major part of the tumor was situated. As each one of these various groups presented different problems, the selection of cases for treatment in this manner must be discussed individually rather than collectively.

Growths at the base of the tongue in the hypopharynx that were part of carcinoma of the body of the tongue were not considered: only primary growths at the base of the tongue in the hypopharynx were included. Growths in this location can be of three varieties: (1) adenocarcinoma, mixed tumor type which is usually a low grade tumor; (2) highly malignant squamous cell epithelioma of grade 3 or 4 that infiltrates into the tongue and that is an active growth, and (3) squamous cell epithelioma of low grade which does not infiltrate into the tongue but is an outgrowth from the surface of the tongue. All of these lesions are best taken care of under suspension laryngoscopy because of the difficulty of obtaining a direct view of them in a satisfactory way with any other method. Only an extensive lesion or extensive metastasis would prevent treatment in this group of cases.

The supraglottic growths consisted of those which involved the epiglottis alone or those that extended into the aryepiglottic fold, base of the tongue, or lateral wall of the pharynx (figs. 1 and 2). Care should be taken not to attempt to treat lesions in this region under suspension laryngoscopy when lateral or subhyoid pharyngotomy which gives much better exposure for the larger growths is indicated. However, many lesions, particularly the highly malignant tumors, that cannot be removed by purely surgical procedures, can be treated with the aid of suspension laryngoscopy (figs. 3 and 4).

In our series the intralaryngeal growths selected for treatment under suspension consisted of tumors of low grade or those of limited extent on the anterior two-thirds of the vocal cord; frequently a thickened leukoplakia with

FIG. 3 — A man, aged sixty years, with squamous cell epithelioma grade 4 of the epiglottis and base of the tongue. This was removed after preliminary tracheotomy, July 2, 1934, and radium points were inserted into the growth. The patient has had no recurrence for six years.

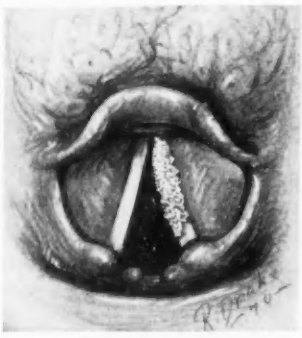


FIG. 5 — A man, aged forty-four years, with squamous cell epithelioma grade 2 at the base of a leukoplakia along the anterior two-thirds of the left vocal cord. This was removed November 20, 1936 under suspension laryngoscopy, using surgical diathermy, with no recurrence for three and a half years.

FIG. 4 — Same case as figure 3 (×200).

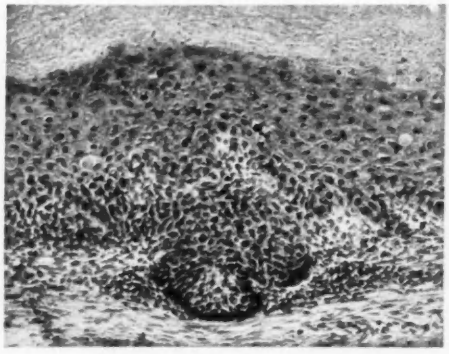


FIG. 6 — Same case as figure 5 (×180).

early epithelioma was taken care of in this manner (figs. 5 and 6). In elderly patients, particularly those with hypertension, diabetes, or bronchiectasis, for whom the risk from thyrotomy is increased, removal of the lesion by intralaryngeal methods is justified if the lesion is small, of low grade, and there is no fixation of the cord.

The growths, involving the lateral and posterior walls of the hypopharynx, are usually highly malignant tumors. They can be treated by the insertion of radium seeds into the lesion as well as by external irradiation. Tumors of the highly malignant type can be treated more successfully with radium than low grade tumors; consequently, small lesions of low grade should be removed with surgical diathermy.

Of the postcricoid growths only two have been treated in this series with the aid of suspension laryngoscopy. In most of these cases roentgen therapy with fractional doses accomplishes as much as any local treatment of the growth. It

is only in the low grade lesions that we feel that external operation, by the method of Trotter in which lateral pharyngotomy is performed, gives the patient any permanent benefit.

REVIEW OF CASES

The average age of the thirty-eight patients was 57.4 years. The youngest was a woman, aged twenty years, who had squamous cell epithelioma grade 2 of the middle third of the vocal cord, and the oldest was a man, aged seventy-nine years, who had squamous cell epithelioma grade 4 of the base of the tongue.

There were four women in this group; the ratio of males to females being 8.5:1. Three patients (7.9 per cent) had syphilis.

Ten lesions were situated at the base of the tongue, twelve were in the supraglottic region, eleven in the intralaryngeal region, three on the lateral and posterior walls of the hypopharynx, and two in the postcricoid region (table 1).

The most common symptoms in this group of cases were dysphagia and hoarseness. The symptoms, of course, depend on the location and extent of the lesion. Malignant lesions at the base of the tongue are frequently overlooked. The advanced lesions produce marked symptoms of pain, bleeding, and so forth, while the early lesions produce little discomfort. On this account, patients with epithelioma of the base of the tongue, epiglottis and aryepiglottic fold usually have large lesions at the time of the first examination. Patients with early lesions of the supraglottic region frequently complain of a sensation of a foreign body in the throat while those with lesions on the vocal cords have hoarseness early, and frequently the lesions are small. Only three patients noticed enlarged glands in the neck, although eight patients were found to have enlarged glands in the cervical region at the time of examination.

THE METHOD OF TREATMENT

Pentobarbital sodium, 1½ grains (0.1 gm.), was administered by mouth an hour before the operation. The larynx was cocainized with a 10 per cent solution of cocaine, and the patient was then anesthetized with sodium ethyl (1-methylbutyl) thiobarbiturate (pentothal sodium) given intravenously. A 2.5 per cent solution was used. A pharyngeal tube was inserted into one of the nostrils through which oxygen was administered throughout the procedure. The pentothal sodium was administered intermittently whenever necessary.

TABLE I.
38 CASES OF MALIGNANT LESIONS OF THE HYPOPHARYNX AND LARYNX 1927-1937 INCLUSIVE.
Location of Lesion.

SITE OF LESION	PATIENTS		LENGTH OF LIFE AFTER TREATMENT (YEARS)	
	Total	Living Last Report; No Recurrence	Greatest	Average
Base of Tongue	10	5	5	4.7
Supraglottic region	12	8	9.5	5.8
Intralaryngeal region	11	9	4	3.6
Hypopharynx, posterior and lateral walls	3	0	7*	
Postericoid region	2	1	7.5	
Total	38	23	9.5	4.8

*Died of recurrence.

A flat spatula attached to the suspension apparatus was employed for the lesions at the base of the tongue. For lesions of the epiglottis the spatula picked up the base of the tongue and exposed the entire epiglottis and vallecula. For intralaryngeal lesions the spatula picked up the epiglottis, and the surgeon had a direct view of the entire glottis. In all cases a specimen of the lesion was removed, a fresh frozen section was examined, and immediate diagnosis was made. Results of microscopic examination of the tissue removed are given in table 2.

In cases of carcinoma of the base of the tongue and epiglottis or aryepiglottic fold, preliminary tracheotomy was performed. After recovery the laryngeal suspension was done, and treatment was performed. For growths involving the base of the tongue (figs. 7 and 8), radium emanation seeds were inserted into the lesion after the use of surgical diathermy. If the lesion was of limited extent, the entire treatment was completed with surgical diathermy alone. The supraglottic lesions were destroyed with a long protected diathermy point. This is a long needle covered with Duco varnish so that only the distal end of the needle is exposed. The epiglottic growths were

FIG. 7 — A woman, aged seventy years, with lymphosarcoma of the base of the tongue at the level of the epiglottis. This was partially destroyed with diathermy on June 17, 1936, and radium points were inserted into the growth. She has had no recurrence for four years.

TABLE II.

38 CASES OF MALIGNANT LESIONS OF THE HYPOPHARYNX AND LARYNX 1927-1937 INCLUSIVE.

Histologic Type.

LESION	HISTOLOGIC GRADE	PATIENTS		LENGTH OF LIFE AFTER TREATMENT (YEARS)	
		Total	Living Last Report; No Recurrence	Greatest	Average
Squamous cell epithelioma	1	4	3	3.8	3.3
	2	9	8	5.0	4.0
	3	9	4	9.5	7.2
	4	7	3	6.5	4.2
Mixed adenocarcinoma and squamous cell epithelioma	3	1	0	6.5*	
	4	1	0	6.5†	
Hemangio-endothelioma	1	2	1	9.5	6.2
Mixed tumor		2	1	5.0	
Lymphosarcoma		2	2	4.0	3.9
Fibrosarcoma	1	1	1	9.0	
Total		38	23	9.5	4.8

*Died of malignancy.
†Died of carcinoma of the stomach.

removed piecemeal (or in one piece) with the Bovey surgical diathermy unit. The intralaryngeal lesions were removed with the diathermy point. No attempt was made in the primary laryngeal lesions to use radium in addition to diathermy except in unusual circumstances, for we felt that lesions extensive enough to need radium in addition to diathermy are better treated by means of thyrotomy.

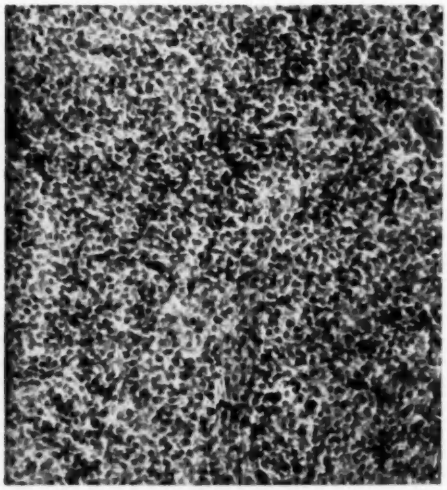


FIG. 8 — Same case as figure 7 (×200).

In addition to treatment under suspension, radium or roentgen rays were applied to the outside of the neck, especially in cases of highly malignant growths at the base of the tongue.

RESULTS

The results of the treatment of malignant disease of the hypopharynx in the past have been very poor. The Trotter operation has produced some very striking results, but they are few. Recently fractional doses of roentgen rays as well as radium used externally have been of considerable benefit. Lenz[2] in discussing Martin's paper reported thirty-one cases of hypopharyngeal malignancy; six (19.3 per cent) of his patients were apparently free of disease, but the length of time these patients have lived since treatment was not stated. Four of these patients had growths involving the epiglottis.

FIG. 9 — A man, aged forty-five years, with squamous cell epithelioma grade 4 of the entire base of the tongue and a large metastatic mass measuring 2.5 by 2.5 by 3.5 cm. in the cervical region. Under suspension laryngoscopy, August 2, 1933, radon seeds were inserted into the growth. This was followed by roentgen treatment applied externally to the neck. The patient is alive and well and without recurrence seven years after treatment.

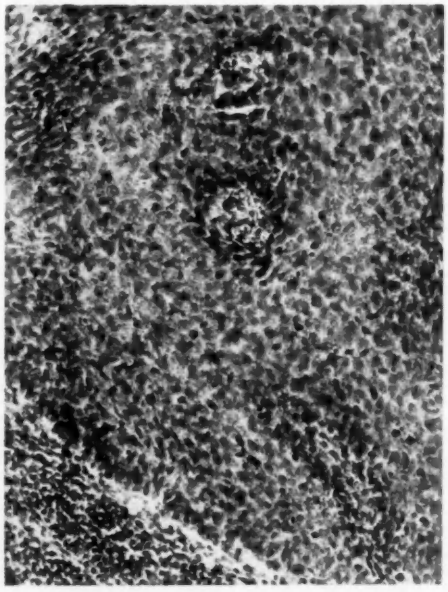


FIG. 10 — Same case as figure 9 (×190).

Of the twenty-seven patients with malignant disease of the hypopharynx including the base of the tongue (figs. 9 and 10), supraglottic region, lateral and posterior walls of the hypopharynx, and postcricoid region, we were able to trace twenty-six, and fourteen (or 51.8 per cent) of the patients who were traced were alive and well.

Of the eleven patients with intralaryngeal lesions, ten were traced and nine (or 90 per cent) were alive and without recurrence. These patients had small, low grade lesions which accounts for this very high percentage of cures.

Nine of the traced patients (or 25 per cent) died of cancer, the majority within a year and a half of the final treatment. One of the group now dead lived seven years, and one six and a half years.

There was one postoperative death; the patient died of bronchopneumonia eight days following treatment of an epithelioma at the base of the tongue. This patient did not have a preliminary tracheotomy.

The three and five year survivals are shown in table 3. Of thirty-one patients treated and traced for three or more years (operations were performed in 1936 or before), twenty-three (or 74 per cent) lived more than three years. Of seventeen patients treated and traced for five years (operations were performed in 1934 or earlier), ten (or 59 per cent) lived more than five years. In the series there were three patients who have lived more than nine years following treatment, and all of these are living at the time of this report (1940).

TABLE III.
MALIGNANT LESIONS OF THE HYPOPHARYNX AND LARYNX.
3 and 5 year Survivals.

PERIOD AFTER TREATMENT	PATIENTS TREATED*	PATIENTS TRACED	SURVIVED BEYOND INDICATED PERIOD	
			Number	Per Cent.
3 or more years	31	31	23	74
5 or more years	17	17	10	59

*The 3 year group comprises the patients treated 3 or more years prior to the time of inquiry, that is, 1936 or earlier; the 5 year group comprises the patients treated 5 or more years prior to the time of inquiry, that is, 1934 or earlier.

REFERENCES

1. Killian, Gustav: Suspension larynogscopy. Clin. J. 44:89-104 (Mar. 24) 1915.
2. Lenz, Maurice: Discussion. Radiology. 34:161-163 (Feb.) 1940.
3. Lynch, R. C.: Cancer of the larynx. Illinois M. J. 54:40-44 (July) 1928.
4. Thomson, St. Clair: The history of cancer of the larynx. J. Laryng. and Otol. 54:61-87 (Feb.) 1939.
5. Trotter, Wilfred: Malignant disease of the hypopharynx and its method by excision. Brit. M. J. 1:510-513 (Mar. 19) 1932.

DISCUSSION

FRANCIS E. LEJEUNE, M.D., New Orleans: Having been associated for many years with an ardent exponent of suspension laryngoscopy, it is but natural that I should be equally enthusiastic in the use of this method. For many years I have preferred suspension laryngoscopy in the greater part of my laryngeal surgery, and I concur with Doctor New in his statement "the value of suspension laryngoscopy in the treatment of malignant disease of the hypopharynx and larynx is not generally known and appreciated."

Doctor New has emphasized that suspension laryngoscopy is used only in a selected group of cases. This fact is so important that it bears repetition at this time In considering intralaryngeal surgery, only those cases manifesting an early intrinsic lesion on one cord are considered suitable for this type of operation. If the lesion is more extensive, a more formidable procedure must be considered.

In my estimation, suspension laryngoscopy is of greatest benefit in those cases of early intrinsic carcinoma of the larynx where intralaryngeal dissection is done with the knife and forceps followed by coagulation dia-

thermy. By this method the malignancy is successfully eradicated, and the continuity of the larynx is preserved. It is obvious that this type of intralaryngeal surgery will be successful in only selected cases.

Complete relaxation of the patient is essential for the proper exposure of the hypopharynx and larynx. Relaxation is readily obtained by administering pentothal sodium, and with this type of anesthesia it is possible to use coagulation diathermy.

It is gratifying to note that Doctor New reports that 90 per cent of the patients upon whom he has operated for intralaryngeal lesions are alive and have had no recurrence after a period of four years, when this survey was made.

Suspension laryngoscopy permits a better direct exposure of the hypopharynx and larynx than it has been possible to obtain with any other method. With both hands free to operate, surgery of the hypopharynx and larynx has not only been simplified by this method, but the favorable results from intralaryngeal surgery have been increased considerably. Suspension laryngoscopy has proved so valuable and indispensable to me that I feel this method should be generally adopted.

(Moving pictures.) This first illustration reveals an early carcinoma on the lingual surface of the epiglottis. This was removed, and the base was treated by coagulation diathermy. The patient remains perfectly well after a period of six years. Unfortunately, these pictures are all in black and white.

This next illustration simply shows the visualization that is possible by suspension laryngoscopy for a suspicious lesion which involves possibly the cricoid area. This represents a large area, carcinomatous in character, of the entire mouth of the esophagus. You will notice that the arytenoid regions and arytenoids themselves show early infiltration, while there is no involvement whatsoever of the larynx itself. The vocal cords move normally and easily. Of course, this is an inoperable case. It was impossible to do anything for this patient besides extensive irradiation, which did not prove beneficial.

The view obtained here is such an unusual one that I am presenting it more for observation than for anything else.

Doctor New mentioned in his presentation something about supraglottic tumors. I was fortunate in having such a case, and, therefore, I would like to present it. Here is the large tumor, covering over and obliterating the entire larynx. It is attached to the aryepiglottic fold. There was a partial capsule, and it was possible to dissect this tumor, following which the entire base of the tumor was coagulated. This is a view of the larynx and the area which the tumor had occupied, which was taken immediately after dissection. The entire area was coagulated with coagulation diathermy, and the patient remained well four and one-half years following the operation, at which time she developed pneumonia and died.

The successive views simply show the exposure which is possible on occasions with suspension laryngoscopy and how easy it is to reach these areas for diathermic coagulation or for surgery.

Following this procedure, naturally there was a complete fixation of the right arytenoid, but at no time during the four and one-half years was there a recurrence. This woman, of course, had radiation in addition to the removal of the tumor and coagulation.

HARRIS P. MOSHER, M.D., Marblehead, Massachusetts: When you hear a Mayo paper (and this paper by Doctor New and Doctor Dorton is a typical one), you are crushed, momentarily always, permanently often. This is due to the overwhelming number of cases reported and the good results of the cases; to the brevity and the sticking-to-the-point in the writing; to the superb illustrations and the readable legends. I have often wished, however, that the Mayo Editorial Board would take a little of the chill of perfection from the papers.

The writers gave Lynch full credit for this work in suspension laryngoscopy. He treated malignant disease of the larynx in many cases with the aid of suspension laryngoscopy. Lynch did not have the help of the modern use of radium, x-ray, and of diathermy.

The method never gained in popularity. Doctor New finds it only of limited use, since in 450 cases he used it only 38 times, and of these cases there were only 11 laryngeal cases, or roughly, one in 40 of the total 450.

He is very guarded as to the type of case in which it is to be used, and warns that the cases must be carefully selected. All who have listened to this paper, I am sure, will agree to this.

I agree with what he has to say about cancer of the base of the tongue. The base of the tongue, however, is not always easy to see well. Various widths of spatulas are often necessary in order to pick the one which gives the best field and stays in place. The tongue is still an unruly member, at least with me. You can take this literally if you like.

I am a bit surprised that Doctor New is so lukewarm to lateral pharyngotomy as done by Trotter. The splendid all-around view which it gives of postcricoid growths, especially when the growth is a backward extension from the larynx, has always appealed to me. If the esophagus is involved as well, I consider it the method of choice.

I differ somewhat with Doctor New on the question of dealing with cancer of the larynx by suspension laryngoscopy. In spite of his splendid results, 90 per cent cured cases, I am not convinced of the superiority of suspension laryngoscopy over the results obtained in the same type of case by thyrotomy. The percentage of cures obtained by thyrotomy is the same, 90 per cent. A small low grade tumor on the anterior two-thirds of the cord, especially if it is partially pedunculated and the patient is elderly, would seem to me to be the ideal case for removal under suspension laryngoscopy.

In all tumors of the larynx, especially in small ones, the vital thing to know is whether there is subglottic extension and the amount. This cannot be determined by simply looking at the tumor from above. It is a fundamental principle in surgery to take the shortest route to the objective and the one which gives the fullest view; that is, the best all-around view. In thyrotomy the larynx is literally an open book. In suspension laryngoscopy it is a closed book, and you can read only the top of the page. In thyrotomy the operator sees the whole page from top to bottom, and the most important thing on the page is often at the bottom.

Growths at the anterior commissure often stop over beyond the commissure on both sides. Such cases would be for me particularly hard to deal with by suspension laryngoscopy.

In malignancy of the tongue, Doctor New uses a preliminary tracheotomy as a routine, and I heartily agree with this. In thyrotomy I feel it is essential to use a postoperative nasal feeding tube. Without this safeguard, a mis-swallow on the part of the patient can result in fatal pneumonia, as I know from personal experience.

To sum up, as I see it, the whole issue between suspension laryngoscopy and thyrotomy in treating malignant disease of the larynx is: (1) which gives the fuller view, (2) which is the shorter route, and (3) which permits more thorough work when the anterior commissure of the larynx is involved? Thyrotomy in my opinion, in all these points, is superior to suspension laryngoscopy. It would bother my surgical conscience, insofar as I have one, if I used, in malignant disease of the larynx, suspension laryngoscopy except in the exceptional case. From my understanding of the paper, this is what the writers advise.

GORDON B. NEW, M.D., Rochester, Minnesota: I have tried to emphasize the fact that this method should be used only in selected cases. The group I reported extended over a eleven year period, and during that time there were only ten cases of intralaryngeal cancer treated by this method.

A woman, seventy-eight years old, who was a poor surgical risk with a low grade epithelioma without fixation involving the middle third of one vocal cord was treated by removal of the growth under suspension laryngoscopy. I feel that this method is very valuable in older patients such as this one who might not do well if a thyrotomy were done.

Regarding Trotter's work in malignancies of the pharynx, I believe that he did beautiful pure surgical work. When I visited him he did not use surgical diathermy or irradiation in these cases.

I feel that the method I have outlined has many advantages in certain selected cases rather than putting the patient through a major operative procedure. I want to emphasize again the fact that this is not a method of treating all cancer of the larynx and pharynx but should be limited to selected cases as I have mentioned.

CANCER OF THE LARYNX: ITS INCREASING INCIDENCE

CHEVALIER JACKSON, M.D.
and
CHEVALIER L. JACKSON, M.D.
PHILADELPHIA

THE INCIDENCE of malignant neoplasms is no quodlibetic subject. In fact no phase of it could be truthfully so called, inasmuch as no one can say today what bearing any kind of study may have on the ultimate solution of the many problems presented by these diseases. Incidence is always regarded as important in the search for etiologic factors, and knowledge of etiology is usually fundamental to prophylaxis. It seems not unreasonable to hope that some day the researches of the medical profession will add cancer to the list of achievements of the profession in preventive medicine.

A study of the trend of incidence of cancer of the larynx seems of particular importance because of the opinion generally held among clinicians that cancer deep in the respiratory system is of increasing frequency.

From the viewpoint of the laryngologist, especial importance is attached to a study of incidence of cancer of the larynx because of the fact that early intrinsic laryngeal cancer is curable, now, in about 80 per cent of the cases.[5] When it was regarded as one of the curiosities of medicine, neoplastic malignant disease in this region was always, in its curable stages, mistaken for chronic laryngitis. Once a disease is recognized as common, it is seldom diagnostically overlooked because all practitioners are alert to its possibility. In cancer of the larynx this would mean recognition in its curable stage.

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6-10, 1940, Cleveland, Ohio.

Search of the literature reveals little information on the relative incidence of cancer of the larynx and almost nothing on the trend of incidence. It is unfortunate that vital statistics, conforming with the International List of Causes of Death, have grouped the larynx with the respiratory system, omitting detailed sites. At best, vital statistics show only mortality. This is a fair criterion of incidence in an anatomical region like the esophagus where the mortality is practically 100 per cent, but in a region like the larynx where cancer curability is potentially 80 per cent, mortality statistics are not a fair criterion of incidence.

It is hoped that this paper will help to draw attention to the necessity for two things, namely, the recording of the incidence as distinguished from mortality of cancer of the larynx, and separate recording of endolaryngeal cancer as of a particular site.

With a view to brevity and clarity of presentation of the phases of the subject considered here, the word cancer and cognate words are used to include all malignant growths.

It is our purpose in this paper to present data, some of which have been hitherto unpublished, bearing on the incidence of cancer of the larynx with comparative data bearing on the trend. Before taking up the subject of the laryngeal phases, it seems important to say something relative to the incidence of cancer in general and especially of pulmonary cancer.

INCIDENCE OF CANCER IN GENERAL

Gross statistics pertaining to cancer, which include data concerning cancer of all regions of the body, show a progressive increase in mortality from this disease. This increase is well shown by the following data of the Federal Bureau of Vital Statistics:[10]

TABLE I.

1920	1921	1922	1923	1924	1925	1926	1927	1928	1929
72,931	76,274	80,938	86,754	91,138	95,504	99,833	103,578	109,770	111,569
1930	**1931**	**1932**	**1933**	**1934**	**1935**	**1936**	**1937**	**1938**	
115,265	118,141	122,739	128,479	134,428	137,649	142,613	144,774	149,214	

Deaths from Cancer and Other Malignant Tumors: 1920-1938.

The foregoing record of deaths from cancer in the entire registration area of the United States shows a steadily progressive increase in incidence of cancer during the 18 years ending 1938. Unquestionably there was an increase of population during this period (averaging over a million annually); therefore, the first equation to apply is that of increased population, by calculation of the mortality rate per 100,000 of population. Using for this purpose the estimate of the Census Bureau gives the following:[10]

TABLE II.

1920	1921	1922	1923	1924	1925	1926	1927	1928	1929
83.2	85.6	86.2	88.7	91.1	92.8	95.1	95.7	96.1	95.9
1930	**1931**	**1932**	**1933**	**1934**	**1935**	**1936**	**1937**	**1938**	
97.3	98.9	102.0	102.2	106.2	107.9	111.0	112.0	114.6	

Number of Deaths from Cancer per 100,000 of Population, (U.S.A.)

The increase shown in these statistics is so evenly progressive, and the statistics are on such a large scale, that it seems logical to regard them as significant of increase of cancer mortality.

Age is such an important etiologic factor in cancer that the age composition must be considered in the equation of adjustment. This has been given proper consideration in all of the statistics presented here.

Mary Gover[3] quotes from data compiled from tabulations made by the Bureau of Census:

> Recorded mortality from all cancer has increased, when the changing age composition of the population has been taken account of, from 68.3 in 1900 to 120.6 in 1935, in the registration states of 1900.

We believe that there is no valid reason for doubting that the disease we all know as cancer is steadily and progressively increasing.

INCREASED INCIDENCE OF CANCER OF THE LUNG

It seems important to study incidence of cancer of the lung in relation to cancer of the larynx, not because of lymphatic or vascular connections, but rather because both these regions are parts of the same system — the respiratory; and especially because of their exposure to the same group of suspected cancerigenic substances taken in with the inspired air. It has been proven that coal tar and coal soot can, under certain circumstances, produce cancer of the skin.

There is an abundance of statistical evidence that cancer of the lung occurs much more frequently in men than in women. Ewing[1] quotes Stout as giving the proportion as males 83 per cent, females 17 per cent. This preponderance in cancer of the lung occurring in the male sex is curiously parallel to a similar preponderance in cancer of the larynx.[5,6]

This is not the place for discussion of the question as to increased incidence of cancer of the lung. We shall therefore cite authorities.

Morris Fishbein, in an editorial[2] from the broad viewpoint of the literature of the subject, states:

> Cancer of the lung seems unmistakably to be steadily increasing in frequency. This increase, both relative and absolute, cannot be explained as being solely due to improvement in diagnostic technic and to more careful postmortem studies.

As quoted here subsequently in full context, James Ewing[1] states:

> The impression of clinicians should be accepted that the disease [cancer of the lung] has increased markedly in the past two decades, from 1920 to 1940.

These matters are discussed in a subsequent paragraph, and some significant data are given in table 8.

Relative Incidence of Cancer of the Lung and of the Larynx. — The relative incidence as between these two parts of the respiratory tract is important. Mary Gover[3] states:

> Considering cancer of the respiratory organs, the annual increase in the rates for cancer of the lungs and pleura has been considerably higher than for cancer of the larynx. The increase for both sites has been more among males than among females; and also more from 1914 to 1931 in the registration States of 1914 than from 1925 to 1935 in the registration States of 1900. Since 1925 there has been no increase in the rate for cancer of the larynx among females in the registration States of 1900.

INCIDENCE OF CANCER OF THE LARYNX

Search of the literature reveals but little that is useful concerning incidence of cancer of the larynx and only two articles devoted to increased incidence. A few articles give general statements of opinion based on personal experience.

James Maxwell and J. Cecil Hogg[8] from a study of the cancer mortality statistics of England and Wales, which include, in addition to the larynx itself, the pyriform fossa, epiglottis, postcricoidal region, and trachea, reach the following conclusion:

> Study of the yearly incidence shows that there has been a steady increase in the number of cases reported annually, and that the figure for 1930 is considerably more than twice that for 1911. The proportion of all cancers which arose in the larynx is also seen to have mounted steadily from 1.29 per cent to 1.92 per cent [of all cases of malignant growths].

Kennaway and Kennaway[7] in a study based on 9,472 death certificates in cases of cancer of the larynx, during the period from 1921 to 1932, found that there had been an increase from 641 to 902 cases per annum in males, 138 to 243 in females.

Data Received from Members of This Society. — We are greatly indebted to the members of the American Academy of Ophthalmology and Otolaryngology who have been so helpful in sending us data on the incidence of cancer of the larynx. The mass of material is so great that it can be alluded to only collectively and after complete analysis. This will be done later; but two outstanding features may be mentioned here. These data, covering over 2,700 cases, indicate clearly that cancer of the larynx is today a relatively common disease. When we compare this with the statements of laryngologists of prior generations who regarded it as quite rare, we have general evidence to add to statistical evidence that the incidence of cancer of the lar-

ynx is increasing. Difference in diagnostic skill of the two periods cannot be considered as an important equation in this connection, because even if the laryngeal cancer were overlooked early in its course, it would inevitably have been discovered later.

The other point demonstrated by these replies is that many patients treated for cancer of the larynx are cured and live to die of other diseases. This emphasizes the point, elsewhere herein mentioned, that mortality records are not a fair criterion of incidence of cancer of the larynx; therefore, this discrepancy must be offset against the underreporting of any previous period in determining the equation of adjustment in statistics.

Available vital statistics show a progressive increase in incidence of cancer of the larynx. Before this apparent increase can be accepted in all its implications, an equation of adjustment, so far as determinable, should be applied. Some of the factors in this equation are the following:

1. Shortcomings in statistics.
2. Increase and changes in age distribution of population.
3. Increase in longevity.
4. Greater and earlier opportunity for skilled laryngeal examination now as compared to any former period.
5. Primary laryngeal cancer recorded after extension as pharyngeal or esophageal cancer.
6. Date selected for comparison; only recent years afford dependable data.
7. Inaccuracy of diagnosis without biopsy or autopsy.
8. Determination of importance of this inaccuracy now and that of any former time used as a basis for comparison.
9. Relative increase of cancer in other regions of the body.
10. Various other factors of less importance.

Shortcomings in Statistics. — Before going far into the study of the questions to which answers are desirable it becomes obvious that all hope of even approximate mathematical accuracy must be abandoned. Some of the reasons for this are the following:

(*a*) Though the death rate per thousand of population is now relatively quite accurate, if we wish to compare recent records with those of earlier years, we are confronted with the fact that prior to a few decades ago deaths from any cause were systematically recorded in many states only in cities. In 1900 only eleven states were included. Today one state, Texas, still remains omitted.

(*b*) Vital statistics on phases other than simply the death rate are subject to a large equation of adjustment.

(*c*) Even today there is a deplorable lack of data bearing on cancer incidence as distinguished from cancer mortality. This makes but little difference in relation to involvement of regions in which the mortality of cancer is close to 100 per cent; for example, in the esophagus. In the larynx, where cancer is curable in 82 per cent of the early cases, there is a wide difference between cancer incidence and cancer mortality, and this difference is widening steadily as the frequently malign nature of persistent hoarseness is becoming more generally recognized by the laity.

(*d*) As elsewhere stated[5] many of the deaths from cancer of the larynx are unrecorded as such in vital statistics because at time of death, extension of the disease to the pharynx led to recording laryngeal cancer deaths among the deaths as a result of cancer of the pharynx. This pertains to the records of today though not to the great extent that prevailed in the days when the diagnosis of cancer of the larynx was never made

early because of lack of laryngeal examination and biopsy.

(*e*) Adding to the difficulties of analysis is the fact that in many statistical tables cancer of the pharynx is grouped with cancer of the esophagus. Doubtless many primary laryngeal cases are thus hopelessly buried. Then came the International List of Causes of Death, grouping diseases of the larynx with diseases of the respiratory tract. This is logical enough, but when we wish separately to study the trend of incidence of cancer of the larynx it is misleading to include pulmonary cancer. It may be added here that it is improbable that many cases of cancer of the larynx were recorded under regions invaded by metastases from primary laryngeal cancer because patients with this disease rarely have fatal metastases; it may also be added that the larynx is rarely the site of metastatic lesions from remote foci.

(*f*) Unquestionably, until recent years diagnoses of laryngeal disease were made inferentially by general physicians, because few practitioners could examine the larynx. It is obvious that records based on a diagnosis of disease of the larynx made without laryngeal examination, biopsy, or autopsy are not only valueless but would be directly misleading. Only a small proportion of deaths by cancer are based on autopsy diagnoses in the United States. Even in approved hospitals perhaps not more than half the diagnoses in fatal cases of disease are based on autopsy findings. For nearly two decades biopsies were not done because there was prevalent a fallacious theory that taking a specimen caused dissemination.[5]

Increase in Population and Changes in Age Distribution. — As hereinafter mentioned, the factor of increased population is satisfactorily eliminated from the equation by using 100,000 population as a basis for calculation. Age composition is not quite so satisfactorily adjusted in statistics, but it has been done approximately.

Increase in Longevity. — The death rate from cancer is of course necessarily in close relation to age. The average age of a population varies somewhat, but on the whole it has been steadily though slowly rising. In the United States the median age of the entire population was 18.8 years in 1850; 25.2 in 1920; 26.4 in 1930; 27.6 in 1935. Much of the increase in longevity has been due to preventive medicine. A large part of the increase has been the result of the work of the medical profession in reducing the death rate in infancy. This part of the increase should not be considered deductable from the increasing cancer trend because mortality from cancer in the first two decades of life is negligible. Therefore, it seems logical to regard increasing longevity as a small factor in the deductible equation to be applied to the increasing cancer trend. Nevertheless all of our statistics are adjusted for change in the age composition of the population.

It is a satisfaction to note that since 1930 statistics of cancer, based on site, are available; and there will certainly be greatly increased accuracy in the records of all phases of cancer including cancer of the larynx. Comprehensive data on the incidence, as distinguished from mortality, of cancer of the larynx is much to be desired, but is today totally lacking.

Laryngeal Examinations. — Unquestionably laryngologists were not easily available for quite a large percentage of the rural population a few decades ago; but certainly by taking the statistics of say the last five years as a basis this factor is enormously reduced. Every small town has one or more laryngologists, and the ubiquitous automobile has brought small towns within reach of almost all the population.

The importance of all the above mentioned factors is greatly diminished by taking into consideration only the last five years, and this limitation practically eliminates some of them.

DATA ON TRENDS IN INCIDENCE OF CANCER OF THE LARYNX

Notwithstanding all the shortcomings and difficulties frustrating mathematical accuracy, as enumerated in the foregoing, there are statistics on so large a scale that the equation of error is greatly diminished. The most significant of these will be presented here.

In a special report of the Federal Census Bureau, certain significant data are given, and from them we have calculated proportionate incidence as shown in the following table:

could have been little change in longevity. The shortness of the period minimizes practically all the other factors in the equation of adjustment enumerated above. The increase in population during the five year period cannot be approximated until the 1940 census returns are fully completed, but there is no reason to suppose there was an increase sufficient to affect the result materially. Cancer of the larynx being a curable disease, the total incidence at this site was greater than given above, but, of course, this equation if known would be equally applicable to all the annual laryngeal totals.

By the courtesy of Dr. Louis Dublin we are able to present data bearing on the trend of the mortality rate among policy holders of the Metropolitan Life Insurance Company. These data are of

TABLE III.

	LARYNX		ALL SITES		TOTAL ALL SITES	TOTAL LARYNX	PROPORTION
Year	Male	Female	Male	Female			
1934	963	137	61,610	72,818	134,428	1100	1:122
1935	987	165	62,933	74,716	137,649	1152	1:119
1936	1069	170	65,545	77,068	142,613	1239	1:115
1937	1083	154	67,349	77,425	144,774	1237	1:117
1938	1197	143	69,857	79,357	149,214	1340	1:111

Deaths from Cancer of the Larynx Compared to Total from Cancer.

The foregoing table (3) seems to us of especial significance. Though the period, five years, is not long, yet these are the most important years from the viewpoint of accuracy. These statistics involve a smaller equation of error than any other available data. The total number of cancer deaths (708,678) eliminates temporary fluctuations in cancer mortality rates. The brevity of the period largely eliminates the strongly stressed improvement in accuracy of diagnosis. It is not logical to suppose that there was any great difference in diagnostic ability between the physicians of 1934 and those of 1938. There

especial value because of their accuracy.

No significant trend in incidence is shown among this selected group of persons. The absolute percentage is small, partly because the age range includes childhood; though it is noteworthy that there was one cancer death under the age of four years and one between 10 and 14.

Through the courtesy of Mr. Carl Voegtlin, Chief of the National Cancer Institute, Bethesda, Maryland, we are able to present here previously unpublished data bearing on the trends of incidence of cancer of the larynx in the registration area of the United States.

TABLE IV.

RACE, SEX AND AGE PERIODS	1939		1938		1937		1936		1935	
	Deaths	D. R.	Deaths	D. R.	Deaths	D. R.	Deaths	D. R.	Deaths	D. R.
Total Persons All Ages	169	1.0	183	1.0	183	1.0	171	1.0	146	.9
Under 1	...	...	...	...	...	...	...	...	...	...
1 to 4	...	...	...	...	...	...	1	.1	...	...
5 to 9	...	...	...	...	...	...	...	...	...	...
10 to 14	...	...	...	...	...	...	...	...	1	*
15 to 19	...	...	...	...	...	...	...	...	...	...
20 to 24	...	...	...	...	...	...	...	...	...	...
25 to 34	...	...	1	*	...	...	1	*	...	...
35 to 44	10	.5	9	.4	10	.5	3	.1	4	.2
45 to 54	30	1.6	47	2.5	47	2.5	44	2.4	37	2.1
55 to 64	69	5.1	72	5.3	61	4.6	82	6.4	58	4.7
65 to 74	58	8.8	50	7.8	62	10.1	37	6.2	44	7.6
75 and over	2	7.5	4	14.9	3	11.3	3	11.2	2	7.8
White Males All Ages	140	2.1	151	2.2	150	2.2	135	2.0	112	1.7
Under 1	...	...	...	...	...	...	...	...	...	...
1 to 4	...	...	...	...	...	...	...	...	...	...
5 to 9	...	...	...	...	...	...	...	...	...	...
10 to 14	...	...	...	...	...	...	...	...	...	...
15 to 19	...	...	...	...	...	...	...	...	...	...
20 to 24	...	...	...	...	...	...	...	...	...	...
25 to 34	...	...	1	.1	...	...	...	...	...	...
35 to 44	8	1.3	3	.5	9	1.4	2	.3	2	.3
45 to 54	27	4.5	38	6.3	38	6.4	31	5.4	30	5.5
55 to 64	52	12.1	62	14.5	53	12.8	68	17.1	42	10.9
65 to 74	51	25.4	44	22.1	48	25.1	32	17.3	36	19.9
75 and over	2	45.9	3	65.2	2	41.3	2	40.0	2	40.4
White Females All Ages	17	.2	19	.2	26	.3	23	.3	29	.3
Under 1	...	...	...	...	...	...	...	...	...	...
1 to 4	...	...	...	...	...	...	1	.2	...	...
5 to 9	...	...	...	...	...	...	...	...	...	...
10 to 14	...	...	...	...	...	...	...	...	1	.1
15 to 19	...	...	...	...	...	...	...	...	...	...
20 to 24	...	...	...	...	...	...	...	...	...	...
25 to 34	...	...	...	...	...	...	...	...	...	...
35 to 44	...	...	3	.3	...	...	1	.1	1	.1
45 to 54	1	.1	5	.5	7	.7	8	.8	6	.6
55 to 64	11	1.5	6	.8	7	1.0	10	1.4	15	2.2
65 to 74	5	1.3	4	1.1	12	3.3	3	.9	6	1.8
75 and over	...	...	1	7.4	...	...	...	...	...	...
Colored Males All Ages	9	1.0	12	1.3	7	.8	9	1.0	4	.5
Under 1	...	...	...	...	...	...	...	...	...	...
1 to 4	...	...	...	...	...	...	...	...	...	...
5 to 9	...	...	...	...	...	...	...	...	...	...
10 to 14	...	...	...	...	...	...	...	...	...	...
15 to 19	...	...	...	...	...	...	...	...	...	...
20 to 24	...	...	...	...	...	...	...	...	...	...
25 to 34	...	...	...	...	...	...	...	...	...	...
35 to 44	1	.6	3	2.0	1	.7	...	...	1	.7
45 to 54	2	1.7	4	3.4	2	1.7	5	4.4	1	.9
55 to 64	4	5.4	3	4.0	1	1.4	2	2.9	1	1.5
65 to 74	2	7.1	2	7.5	2	8.0	1	4.0	1	4.2
75 and over	...	...	...	...	1	33.2	1	35.4	...	...
Colored Females All Ages	3	.3	1	.1	...	...	4	.4	1	.1
Under 1	...	...	...	...	...	...	...	...	...	...
1 to 4	...	...	...	...	...	...	...	...	...	...
5 to 9	...	...	...	...	...	...	...	...	...	...
10 to 14	...	...	...	...	...	...	...	...	...	...
15 to 19	...	...	...	...	...	...	...	...	...	...
20 to 24	...	...	...	...	...	...	...	...	...	...
25 to 34	...	...	...	...	...	...	1	.5	...	...
35 to 44	1	.5	...	...	...	...	...	...	...	...
45 to 54	...	...	...	...	...	...	...	...	...	...
55 to 64	2	1.9	1	1.0	...	...	2	2.0	...	...
65 to 74	...	...	...	...	...	...	1	2.7	1	2.8
75 and over	...	...	...	...	...	...	...	...	...	...

*Less than .05.

Number of Deaths and Death Rates per 100,000 for Cancer of the Larynx. Arranged by race, sex, and age periods. Metropolitan Life Insurance Company; weekly premium-paying industrial business—1935 to 1939.

TABLE V.

Year	Adjusted (b)	Crude	0-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85+
1925	1.00 (d)	....	....	....	....	....	....	....	....	....	....	....
1930	1.13	1.21	.04	....	....	....	.35	2.44	6.00	7.37	8.09	5.25
1931	1.07	1.16	.04	....	.05	.05	.35	1.97	5.17	8.36	7.17	9.11
1932	1.12	1.23	....	....	....	.04	.38	2.32	5.31	8.42	8.16	9.05
1933	1.19	1.31	....	....	....	.11	.44	2.25	5.47	8.82	11.00	6.42
1934	1.17	1.29	....	....	....	.05	.28	2.75	5.10	7.34	12.76	11.46
1935	1.19	1.33	....	....	....	....	.45	2.29	5.18	8.96	12.00	12.60
						MALE						
1925	1.73 (d)	....	....	....	....	....	....	....	....	....	....	....
1930	1.97	2.10	.07	....	....	....	.57	4.30	10.57	12.97	13.96	10.00
1931	1.87	1.99	....	....	.07	.11	.60	3.49	8.86	14.62	13.82	16.54
1932	1.99	2.14	....	....	....	.04	.52	3.93	9.62	15.37	16.43	13.14
1933	2.17	2.34	....	....	....	.15	.78	4.11	10.29	16.23	18.09	16.33
1934	2.06	2.22	....	....	....	.07	.48	4.74	9.11	12.80	22.85	25.96
1935	2.08	2.26	....	....	....	....	.72	3.54	9.43	15.78	22.13	25.71
						FEMALE						
1925	.30 (d)	....	....	....	....	....	....	....	....	....	....	....
1930	.29	.32	....	....	....	....	.12	.49	1.44	2.09	3.14	2.17
1931	.29	.32	.07	....	.03	....	.08	.38	1.50	2.46	1.56	4.29
1932	.28	.31	....	....	....	.04	.24	.64	1.01	1.88	1.16	6.39
1933	.24	.27	....	....	....	.07	.08	.32	.69	1.84	4.98	....
1934	.31	.35	....	....	....	.04	.08	.68	1.14	2.20	4.19	2.10
1935	.34	.39	....	....	....	....	.15	.99	.97	2.54	3.39	4.15

Trend of Mortality from Cancer of the Larynx in the Registration States of 1900.(a)
Specific for Age and Sex, 1925 and 1930-35.
Annual Death Rate per 100,000.(c)

(a) The registration States of 1900 are Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Michigan, Indiana, and the District of Columbia.
(b) Adjusted to the age distribution of the total population of the United States as enumerated in 1930.
(c) Populations used in the computation of rates were obtained by extrapolating the age and sex distribution of the population as enumerated in 1920 and 1930 and applying them to the estimates of total populations for states (1930-1935) as made by the Bureau of the Census.
(d) Rates for 1925 readjusted for age by multiplying the crude rate for all ages for incidence of cancer by the ratio of the adjusted-to-the-crude rate for all cancer.

TABLE VI.

Year	Adjusted (a)	Crude	0-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85+
1930	.82	.83	.01	....	.02	.01	.33	1.62	4.00	5.69	6.54	5.32
1931	.76	.77	.02	....	.02	.04	.28	1.33	3.65	5.88	5.81	4.86
1932	.84	.87	....	....	.01	.04	.38	1.64	3.79	6.33	6.81	7.35
1933	.85	.88	....	....	.01	.04	.33	1.57	3.93	6.18	7.91	5.43
1934	.85	.89	....	....	....	.07	.32	1.64	3.85	5.90	8.19	7.49
1935	.87	.93	....	....	.01	.07	.35	1.74	3.64	6.65	8.00	7.02
1936	.93	.99	....	.01	.01	.05	.35	1.68	4.63	6.01	9.59	5.87
1937	.91	.98	....	....	....	.07	.25	1.68	4.15	6.62	9.66	6.80
						MALE						
1930	1.39	1.42	.02	....	.01	.02	.53	2.73	6.73	9.88	11.41	9.75
1931	1.28	1.33	....	....	.02	.04	.47	2.25	6.18	10.17	9.93	9.59
1932	1.45	1.51	....	....	....	.07	.59	2.81	6.38	11.13	12.27	12.89
1933	1.45	1.52	....	....	.01	.04	.54	2.76	6.93	10.59	12.44	10.16
1934	1.46	1.54	....	....	....	.10	.55	2.88	6.59	10.28	13.81	15.02
1935	1.47	1.57	....	....	.02	.11	.56	2.81	6.32	11.28	13.45	13.15
1936	1.68	1.70	....	....	.03	.07	.54	2.87	7.78	10.76	15.80	11.34
1937	1.57	1.70	....	.01	....	.08	.43	2.96	7.25	11.53	16.35	10.37
						FEMALE						
1930	.22	.22	....	....	.04	....	.12	.40	1.05	1.33	1.96	2.00
1931	.21	.21	.04	....	.02	.03	.09	.33	.93	1.43	1.92	1.31
1932	.22	.22	....	....	.01	.02	.16	.37	1.01	1.36	1.66	3.21
1933	.22	.23	....	....	.01	.04	.12	.29	.73	1.62	3.61	1.90
1934	.21	.22	....	....	....	.04	.09	.31	.93	1.39	2.87	1.87
1935	.26	.27	....	....	....	.03	.13	.60	.80	1.88	2.83	2.45
1936	.26	.27	....	.01	....	.03	.15	.43	1.29	1.13	3.67	1.81
1937	.23	.25	....	....	....	.06	.07	.34	.88	1.57	3.29	4.15

Trend of Mortality from Cancer of the Larynx in the United States. (a)
Specific for age and Sex, 1930-37.
Annual death rate per 100,000. (b)

(a) Adjusted to the age distribution of the total population of the United States as enumerated in 1930.
(b) Populations used in the computation of rates were obtained by extrapolating the age and sex distribution of the population as enumerated in 1920 and 1930 and applying them to the estimates of total populations for states (1930-1935) as made by the Bureau of the Census.

TABLE VII.

YEAR	NORTHEAST	EAST NORTH CENTRAL	SOUTH	WEST CENTRAL	PACIFIC
			MALE		
1930	2.13	1.29	.51	.66	1.63
1931	2.05	1.23	.48	.66	1.03
1932	2.11	2.43	.70	.66	1.48
1933	2.31	1.27	.67	.67	1.42
1934	2.23	1.49	.59	.67	1.27
1935	2.17	1.39	.71	.77	1.69
1936	2.33	1.41	.81	.81	1.81
1937	2.37	1.48	.71	.80	1.65
			FEMALE		
1930	.30	.20	.10	.10	.30
1931	.25	.21	.15	.10	.21
1932	.28	.21	.08	.11	.35
1933	.27	.23	.17	.15	.17
1934	.30	.17	.14	.17	.23
1935	.36	.22	.15	.15	.32
1936	.34	.17	.21	.29	.35
1937	.30	.24	.12	.14	.22

Trend of Mortality from Cancer of the Larynx in Five Geographic Sections of the United States, 1930-37.
Annual death rate per 100,000; adjusted for age (b).

(a)Adjusted to the age distribution of the total population of the United States as enumerated in 1930.
(b)Population used in the computation of rates were obtained by extrapolating the age and sex distribution of the population as enumerated in 1920 and 1930 and applying them to the estimates of total populations for states (1930-1935) as made by the Bureau of the Census.

NORTHEAST	EAST NORTH CENTRAL	SOUTH	WEST CENTRAL	PACIFIC
Maine	West Virginia	Virginia	North Dakota	Washington
New Hampshire	Ohio	North Carolina	South Dakota	Oregon
Vermont	Indiana	South Carolina	Nebraska	California
Massachusetts	Illinois	Kentucky	Kansas	
Rhode Island	Michigan	Tennessee	Montana	
Connecticut	Wisconsin	Georgia	Idaho	
New York	Minnesota	Alabama	Wyoming	
New Jersey	Iowa	Mississippi	Colorado	
Pennsylvania	Missouri	Florida	Utah	
Maryland		Louisiana	Nevada	
Delaware		Arkansas	New Mexico	
		Oklahoma	Arizona	

The States included in each of the five Geographic Sections are given above.

Incidence Relative to Other Diseases of the Larynx. — It has been difficult to obtain large-scale statistics on this point because relatively few of the many laryngeal diseases appear in vital statistics, which record only mortality. Obtainable records pertaining to otolaryngology of dispensaries and private practices seem to indicate that not more than one laryngeal case in a hundred is one of cancer of the larynx. This of course is not the ratio in special clinics devoted to laryngeal disease.

CAUSES OF INCREASED INCIDENCE OF CANCER

It seems not altogether unjustifiable to accept the statistical evidence as indicating that cancer of the larynx is increasing in incidence. If it is increasing, as we believe it is, then there at once arises the question of the cause of the augmentation. If we do not accept the evidence as showing an increase, examination of the situation will, nevertheless, be worth while because of its bearing on the still obscure general question of etiology of malignant disease. These remarks seem especially appropriate because of the noteworthy fact that cancer of the closely related, continously placed, and functionally interlocked tracheobronchial and pulmonary regions stand suspected of similar increased incidence of cancerous processes.

No one has more thoroughly, impartially, and judicially studied the huge mass of literature of cancer than James Ewing.[1] He states (1940):

To summarize the extensive data on causation: It would appear that cancer of the lung causes between 5 and 10 per cent of all cancer deaths; that in spite of the absence of statistical proof, the impression of most clinicians should be accepted that the disease has increased markedly in the past two decades, from 1920 to 1940; and that abundant cause for this increase may probably be found in the increased exposure to many forms of irritating inhalations, among which tobacco, coal tar products, and dusts of many kinds figure most prominently. A suspicion that some unsuspected chemical cancerigenic agents may be involved may be entertained, and this fact together with the large incidence of the disease seems to call for special investigations by private and public agencies into the responsible factors. . . . In mice that had inhaled road dust containing from 2 to 3 per cent of tar, Campbell observed a tenfold increase of adenoma of the lungs. Dust freed from tar gave much less increase, while cigarette smoke and motor gas gave a slight increase. Tobacco smoke is especially incriminated by Roffo, who found spectroscopic evidence of phenanthrene in tobacco extracts, which produced a high proportion af papillomas of the skin. Lehman found that smoking a 5-gm. cigar yields 200 mg. of inhaled tar, while an 8-hour drive 32 feet behind an automobile over a tarred road yields only 1.5 mg. of inhaled tar. The proportion of smokers among patients with cancer of the lung is very high (Roffo).[11]

From our record[5] we can make the parallel statement that the proportion of smokers among patients with laryngeal cancer is very high. The researches of Angel Roffo[11] on the cancerigenic effects of tobacco are very thorough; the results are interesting and important.

This etiological factor is important in relation to study of incidence because the proportion of cancer of the larynx in men is 10:1, in our experience. Among our patients about 95 per cent of the men were smokers of tobacco; none of the women whose case was reported prior to two years ago was a smoker.

Now that smoking among women is becoming deplorably common, it will be interesting to note in the future the relative incidence in women.

The same may be said of alcohol. Our observations lead us to believe that alcohol as a beverage is a cause of cancer of the larynx. This opinion is strongly supported by the results of the investigations by research workers. Kennaway and Kennaway,[7] after study of death certificates of 9,472 cases of cancer of the larynx, stated that occupations concerned with the supply of alcohol have a high incidence of cancer of the larynx. The enormously increased consumption of alcohol since the repeal of prohibitive legislation has had, and in our opinion, will continue to have, an effect in increasing the incidence of cancer of the larynx. We are sorry to say that this applies also to women.

Unquestionably age and sex are etiologic factors in cancer. It is therefore important that these phases of the subject be considered in dealing with incidence.

INCIDENCE RELATIVE TO SEX

Large scale statistics, including those herein given, show conclusively that cancer of the larynx is more frequent in men than in women. Laryngologists are all of this opinion. In our own experience, males preponderate in the proportion of about 10:1.[6]

Portmann and Phillip,[9] citing 3 cases, suggest that incidence of laryngeal cancer is increasing in females, particularly in the young.

Sex incidence in the larynx relative to that of nearby contiguous epithelial surfaces seems especially important.

It is probable that in the foregoing table many cases of cancer of the hypopharyngeal wall of the larynx were recorded elsewhere, probably under the classification of esophageal cancer. Therefore this phase of the table does not show as great a preponderance of postcricoidal cancer in woman as is shown by the statistics of laryngologic clinics, including our own.[5] But this table is an extremely important one because it shows on a large scale that,

whereas incidence of cancer in the mouth and pharynx decreased 3.3 per cent in 4 years, there was a greatly increased incidence (20.9 per cent) of cancer of the larynx during the same period. Adjustments for increase of population and longevity could not affect the result in so short a period as five years, and as before stated it is illogical to suppose there was any great difference in the diagnostic ability of the physicians of 1934 as compared to those of 1938.

determined in future statistics. Progressive improvement in methods of cure, as well as the earlier diagnosis that has resulted from the publicity laryngologists have given to the frequently malign nature of continued hoarseness, has placed cancer of the larynx among those diseases of which mortality is not a fair criterion of incidence.

In total mortality statistics, cancer of the larynx is much less frequent than uterine and mammary cancer. As these

TABLE VIII.

REGION	YEAR	MALE	FEMALE	PROPORTION	BOTH SEXES	CHANGE	PER Cent.
Mouth, pharynx	1934	4064	945	4.3:1	5099		
	1938	4030	901	4.4:1	4931	—168	—3.3
Larynx	1934	963	137	7:1	1100		
	1938	1197	143	8.3:1	1330	+230	+20.9
Lungs, pleura	1934	2631	1246	2.1:1	3877		
	1938	3669	1631	2.2:1	5300	+1423	+37.

The relative incidences between buccal and pharyngeal as compared to laryngeal cancer is shown by the above mortality statistics of the United States.

This table (8) is significant also in showing that the increase in incidence of cancer of the larynx is coincident with an increased incidence of cancer of the lung. This will be commented upon in a subsequent paragraph.

That the increase in number of deaths from cancer of the lung was even greater than from cancer of the larynx in the proportion of 37:20.9 probably would be partly modified by applying the equation of cures. Cancer of the lung, until recent years, had a mortality of practically 100 per cent and its mortality is still probably 90 per cent; whereas cancer of the larynx is potentially 80 per cent curable. A few cures are made annually of lingual, buccal, and pharyngeal cancer. Inasmuch as there are no detailed statistics of cures on the large scale of the mortality statistics given above, we cannot accurately apply any equation of cure.

From every viewpoint as well as that of accuracy it is important that the equation of cures of cancer of the larynx be

gross statistics do not show a very great difference of cancer incidence such as that which exists between the two sexes (women 54.2, men 45.8),[5] we have, in a sense, an explanation of the relative rarity of laryngeal cancer in women. In a sense, and speaking broadly, it may be said that women develop their cancers in organs peculiar to their sex, which deducts from their alloted number of laryngeal cancers.

This would seem clear enough were it not for another, and so far, unexplainable feature of sex incidence. Whereas men are more frequently attacked by intrinsic laryngeal cancer (in the proportion of 10:1 in our statistics)[6] the posterior wall is the site of cancer more frequently in women than in men, the proportion being 7:1 in the records of our clinic.[5] These records are accurate because the exact site was determined by endoscopic examinations. Official statistics do not separately record this region. It is hoped they will do so, because in present statistics cancer of the phar-

yngeal wall of the larynx is, in most instances, recorded under the heading of esophagus. This is especially deplorable because there is an unsolved problem concealed in the fact that cancer of the hypopharynx runs so excessively against the rule that cancer in women is less than in men in those anatomic regions common to both sexes. The difference is especially worthy of study because of the exceptionally great contrast with the incidence on the other side of the party wall that separates the endolarynx from the hypopharynx. Roughly, for illustrative purposes, it may be stated that endolaryngeal cancer occurs in males in a ratio of 10:1 whereas retrolaryngeal cancer occurs in females in a ratio of 7:1. The result is a differential of 17:1. If it were a question of extension by continuity, the anatomic arrangement of the lymph channels in the two regions would help to account for the difference; but, in our record at least, only primary locations are recorded.

In considering etiology and sex incidence we must not overlook the unquestionable fact that the female sex at all ages is, in the aggregate, less subject to almost all forms of endolaryngeal disease than males. The reverse is true of extrinsic cancer especially on the pharyngeal wall of the larynx, as mentioned before. We must also apply the equation mentioned previously, namely, that in the aggregate, women are slightly more subject to cancer in any anatomic region, as compared to men, the proportion being 54.2:45.8.[5]

INCIDENCE RELATIVE TO AGE

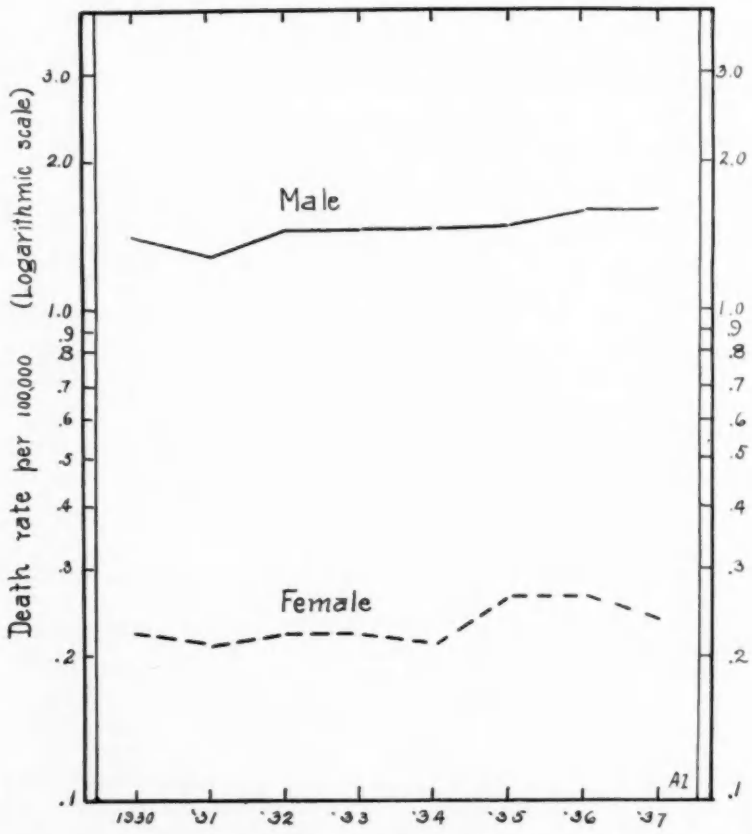
A number of authors (St. Clair Thomson, Negus, McBride, Portmann, Phillip, Garel, Chiari, Mackenty, New, Figi, Orton, Crowe, Broyles, Zinn, Clerf, Martin, Semon, Ferreri, among others) have reported cases of cancer of the larynx in patients under 25 years of age, but none of these authors except Portmann and his co-author Phillip[9] suggest that the incidence among young women is increasing. The bearing of the age composition of the population on statistics has been referred to before under "longevity."

INCIDENCE RELATIVE TO ANATOMIC LOCATION IN THE LARYNX

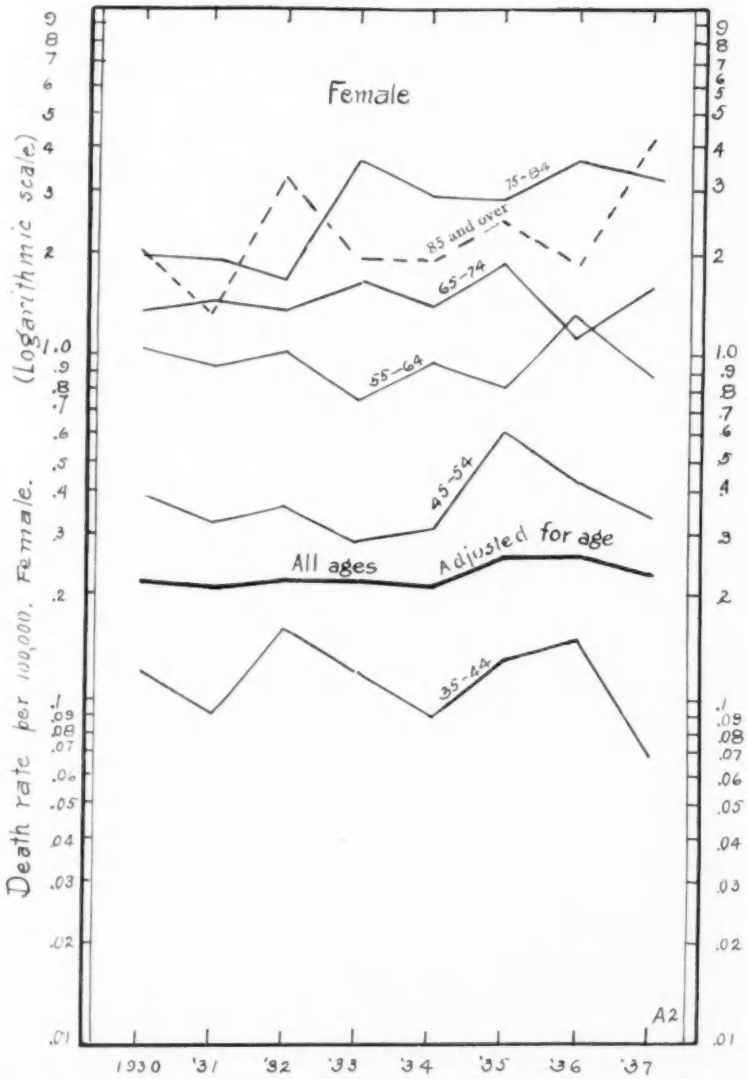
For determination of this point, vital statistics are not only useless but quite misleading. Before a patient dies of primary intrinsic cancer of the larynx, the disease has usually become extrinsic by extension. Therefore, mortality statistics would show almost all laryngeal cancers as extrinsic. Official vital statistics, however, do not distinguish between intrinsic and extrinsic cancer. The clinical records of laryngologic clinics and the individual laryngologists are quite accurate in this respect but there are, as yet, no data from this source that would bear on incidence.

CONCLUSIONS

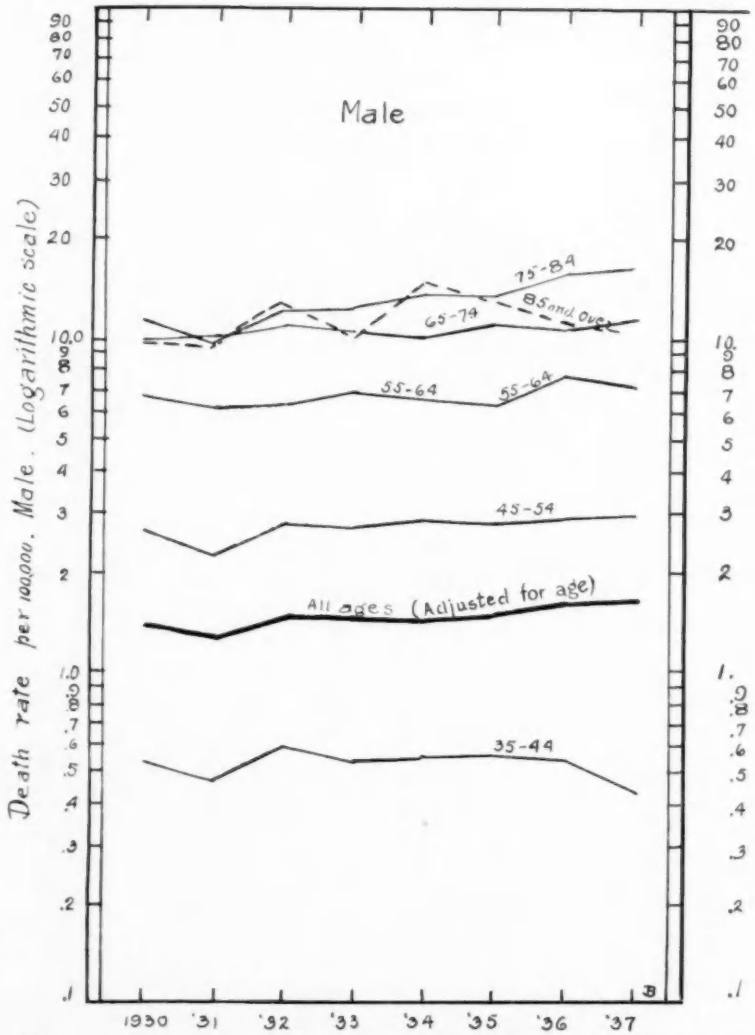
1. One of the most encouraging things revealed by our efforts to collect data is the evidence of a determined effort to obtain, from now on, accurate detailed records of incidence of cancer of the larynx. Such records must inevitably be useful in future studies of this disease; dire if neglected, curable if diagnosed early.
2. In our opinion, the available data, after application of the equation of adjustment so far as the factors of this equation can be determined from available information, warrants the conclusion that there is a small but progressive increase, from year to year, in the incidence of cancer of the larynx.
3. The statistics of a five year period, 1934-1938, have the advantages of: (A) Practical elimination of diagnostic differences. It is not logical to assume that the physicians of 1938



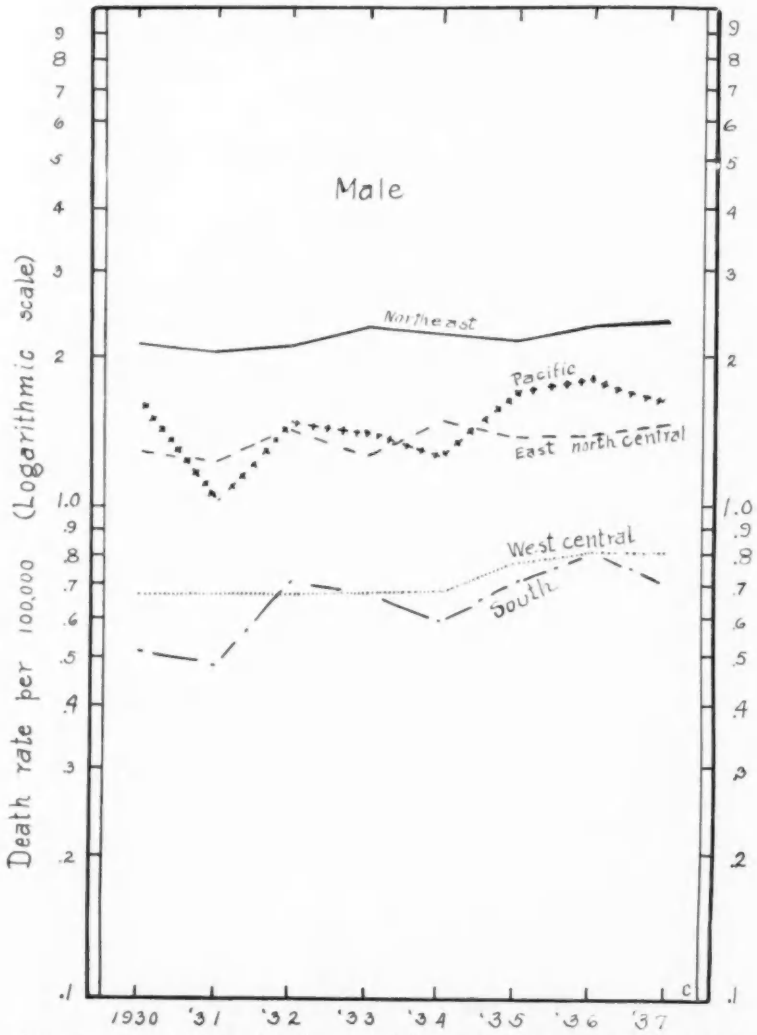
GRAPH A1 — Course of mortality from cancer of the larynx in the United States of America, exclusive of Texas, 1930 to 1937, inclusive (adjusted for age).



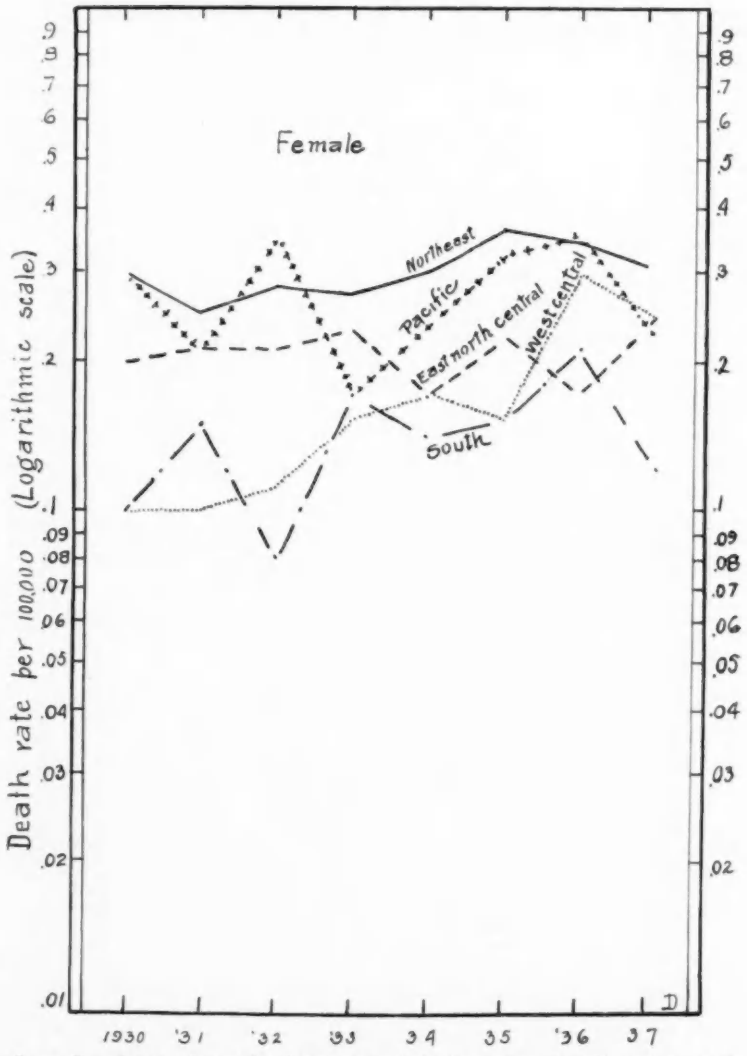
GRAPH A2 — Course of mortality from cancer of the larynx in the United States of America, exclusive of Texas, for specific ages, 1930 to 1937, inclusive (adjusted for age). Female.



GRAPH B — Course of mortality from cancer of the larynx in the United States of America exclusive of Texas, for specific ages, 1930 to 1937, inclusive (adjusted for age). Male.



GRAPH C — Course of mortality of cancer of the larynx, in geographic sections of the United States of America, 1930 to 1937 inclusive (adjusted for age). Male.



GRAPH D — Course of mortality from cancer of the larynx in geographic sections of the United States of America, 1930 to 1937, inclusive. (Adjusted for age.) Female.

were so much more accurate in the diagnosis of laryngeal disease as to make any material difference in comparison to the physicians of 1934. (B) For this short period the adjustments for population, composition of population, and longevity are necessarily small. (C) For these recent years the records are relatively accurate as to mortality.

4. From these records, which are the best data we have, we feel justified in the conclusion that not only is cancer of the larynx steadily increasing in frequency, but that the ratio is increasing.

5. The only large-scale data available are mortality statistics. These understate the incidence because cancer of the larynx is a curable disease; many patients treated for it survive to die of other diseases; and the number cured is unquestionably increasing as shown in clinical records of laryngologists who are members of this society.

6. Therefore, the increased incidence of cancer of the larynx is greater than statistics show.

7. It is interesting to note that the increasing incidence of cancer of the larynx is parallel to the increase of cancer of the lung, a tributary part of the airway. This is noteworthy especially in the study of the problems of etiology and prophylaxis.

8. The cause of the increase in incidence of cancer of the larynx cannot be determined at present. The parallel increase of cancer of the lung suggests a common cause operative on the respiratory system below the level of passages common to food and air. This in turn lends some support to the theory that has been applied to cancer of the lung. If the increase of hours on the highways, and the enormous increase of tarred road surfaces and of gasoline fumes are responsible for increased incidence of cancer of the lung, they would logically be responsible also for the increased incidence of cancer of the larynx. It seems logical to assume that the effect would be even greater on the larynx which stands guard at the entrance to the lower airway.

9. In view of the relatively enormous increase in the use of smoking tobacco by women, and of the hitherto rare incidence of this disease in the female sex, it will be interesting to note the incidence of laryngeal cancer in females during the next decade. The tar and especially the empyreumatic oil of tobacco, present in tobacco smoke, stand suspected as one of the causes of cancer of the larynx and of its trend of increasing incidence. The same may be said of alcohol and its enormously increasing use as a beverage since the repeal of prohibitive legislation.

10. Massive statistics, like astronomic figures, are not easily grasped except by the mathematically minded. Solely for the sake of conveying an easily grasped sense of proportion, we may roughly approximate data as follows:

    About one person in every hundred dies every year.

    About one death in every hundred is due to cancer.

    About one out of every hundred cancer deaths is from cancer of the larynx.

11. One remedy for the increasing incidence of mortality from cancer of the larynx is to educate the public to the fact that persistent hoarseness in an adult calls for immediate examination of the larynx to exclude cancer.

REFERENCES

1. Ewing, James: Neoplastic Diseases, Philadelphia, W. B. Saunders, 1940, p. 527, 873, 913, 914.
2. Fishbein, Morris: Cancer of the Lung, J.A.M.A. 108:1716 (May 15) 1937.
3. Gover, Mary (Associate Statistician): Cancer Mortality in the United States, Monograph, Prepared by Direction of the Surgeon General, 1939.
4. Jackson, Chevalier, and Jackson, Chevalier L.: The Larynx and Its Diseases, Philadelphia, W. B. Saunders, 1937.
5. Jackson, Chevalier, and Jackson, Chevalier L.: Cancer of the Larynx, Philadelphia, W. B. Saunders, 1939.
6. Jackson, Chevalier, and Jackson, Chevalier L.: Cancer of the Larynx, J.A.M.A. 111:1986 (Nov. 26) 1938.
7. Kennaway, N. M., and Kennaway, E. L.: A study of the incidence of cancer of the lung and larynx, J. Hygiene 36:236, 1936.
8. Maxwell, James, and Hogg, J. Cecil: The incidence of laryngeal cancer, Lancet 1:1064 (May 20) 1933.
9. Portmann, Georges, et Phillip, Raymond: L'épithéliome chez les jeunes, Rev. de Laryngol. 54:11 (Jan.) 1933.
10. Report of the Bureau of Vital Statistics, Washington, D. C., 1938.
11. Roffo, Angel H.: Carcinoma desarrollado en el pulmón de rata sometida a los gases de combustión del petróleo, Bol. Med. Exp. para el est. y trat. del Cáncer, Buenos Aires, April, 1939. Also, El tabaco rubio como cancerigeno, Bol. del Inst. de Med. Exp., No. 47, 1938.

DISCUSSION

HAYES E. MARTIN, M.D., New York (by invitation): The Doctors Jackson have presented many interesting statistical data on both the crude and the specific incidence of cancer of the larynx. In interpreting these data they have taken into consideration the fact that a crude increase in the incidence of laryngeal cancer must obviously occur with an increasing population. They have also called attention to the fact that a longer life expectancy must be followed by both a crude and a specific increase in all diseases of middle and old age, and finally — probably the most important of all — they have discussed the increase in the recorded cases of laryngeal cancer due to more accurate diagnosis on the part of the medical profession.

It is not easy to exclude nor to make adjustments for these several variables, each one of which may be rather complex. For instance, let us consider only one interesting aspect of an extended life expectancy. The mean age of patients with cancer of the larynx is about 59 years, while the mean age of patients with cancer of the adjacent nasopharynx is 45 years. Therefore, as life expectancy extends, both the crude and the relative numbers of laryngeal cancers will increase in comparison to cancer of the nasopharynx without the introduction of any new or special etiologic factors.

After discounting these several variable factors, the authors, as I interpret Doctor Jackson's remarks, have concluded nevertheless that a given individual — let us say between the ages of 50 and 60 years — has a greater chance of developing cancer of the larynx today than he would have had ten, twenty-five or fifty years ago. If this could be proved absolutely, it would have great significance in the study of the causation of cancer. However, if such premises were not well founded in fact, one might be led into serious error in drawing definite conclusions from them.

It has been my observation that any physician who specializes in one or another anatomic form of cancer, or in any single disease, is prone to believe that this one particular form is increasing much more rapidly than any other. I heard recently a rectal surgeon give fairly conclusive evidence that rectal cancer was increasing faster than any other, and not long ago I heard a gastric surgeon insisting that cancer of the stomach was increasing faster than any other. So far as the reports of individual laryngologists or institutions are concerned, it must be realized that neither their individual nor their collective experiences are statistically significant since the number of cases which they see will vary mainly in proportion to their interest in the subject and their reputations for successful treatment.

The Doctors Jackson have called attention to the fact that cancer of the extrinsic larynx, which may fail to produce hoarseness at any time during the course of the disease is, in general, likely to be diagnosed as cancer of the pharynx. If this error could be corrected throughout the entire country, there might be an immediate apparent increase in laryngeal cancer of 200 to 300 per cent. In support of such an hypothesis, I wish to present some figures from the admission records at the Memorial Hospital. We find that cancer of the extrinsic larynx is three times as frequent as cancer of the intrinsic larynx. In most

cases the referring physician, if he has discovered the primary lesion, classifies the growth as cancer of the pharynx. These extrinsic laryngeal cancers, making up three-fourths of the whole, would in many quarters be recorded as cancer of the pharynx or simply as cancer of the throat, and I believe that it is entirely possible that throughout the country as many as one-half of the cases of laryngeal cancer are incorrectly classified and recorded today. When our data must be drawn from such uncertain and unreliable statistics, I believe it is unsafe, even after the most painstaking adjustments, to draw any definite conclusion as to an actual increase in the chance of any one person's developing laryngeal cancer.

I have recently gone over the admission records of the Memorial Hospital with regard both to the crude and relative percentages of laryngeal cancer over a period of the past ten years. The curve is extremely irregular, the number of cases varying as much as 50 per cent, either up or down, from year to year. I have also discussed the relative and specific death rates of laryngeal cancer in New York City with Mr. Thomas J. Duffield, Registrar of Records in our Department of Health. Mr. Duffield has supplied me with statistics, and he states that in his opinion the curve is too irregular and the general trend over the ten year period too indefinite to be statistically significant.

So far as I am concerned, I have no definite conviction either for or against this thesis, but I should urge that caution be used in drawing any definite conclusion on the increased incidence of laryngeal cancer from the statistical data available at this time. It is my opinion that a definite answer to this question must be left to the future when some means has been found to eliminate the numerous uncertainties and variable factors which accompany the present methods of recording both the incidence and the mortality of cancer.

CHEVALIER JACKSON, M.D., Philadelphia: We have nothing to add, except to thank Doctor Martin and to say that we quite agree with him that ultimate decision must be left to the future. We venture to hope, however, that our paper will be a starting point inasmuch as there is no literature up to the present on the increase or the trend — decrease if you wish — of cancer of the larynx. These statistics are as accurate as they can be made today.

GONIOSCOPY IN RELATION TO COMMON GLAUCOMA OPERATIONS

JOHN M. MCLEAN, M.D.
BALTIMORE

GONIOSCOPY, or clinical examination of the angle of the anterior chamber, is a method of study of the glaucoma problem which has as yet received very little general attention. The greater part of our knowledge and teaching about the anatomical condition of the filtration angle in glaucoma is based on histological studies of eyes which have either reached the final stages of the disease or come to grief through serious operative mishap. Excellent studies of the condition of the structures in the angle during the progress of the disease have been made by Troncoso,[12] Thorburn,[10] and others, but, because the results of these studies are not completely in accord with certain preconceived notions, they have not received the attention they deserve.

It is my purpose to discuss a clinical study of the glaucoma problem which has been carried on over the past three years. Particular attention is directed to the condition of the structures in the filtration angle as disclosed by repeated gonioscopic observations. Relatively little emphasis is placed on non-surgical phases of glaucoma because these findings are in general accord with those previously reported by other investigators. Careful consideration is given, however, to the effects of the ordinary glaucoma operations, a phase of the subject which has thus far been seriously slighted.

The gonioscopic studies of Troncoso,[12] Thorburn,[10] Werner[13] and Otto Barkan[1] have shown that anterior peripheral synechiae are not a prerequisite of glaucoma. In contrast with the time-honored teachings from study of morbid anatomy, synechiae are found only late, if at all, in the course of non-congestive or compensated glaucoma and only secondarily, although somewhat earlier and more consistently in the course of congestive or uncompensated glaucoma. The findings in our clinic are in complete agreement. Out of 66 cases of non-congestive glaucoma (Table I) there were no synechiae in 49, or 74.3 per cent; minor adhesions in 15, or 22.7 per cent; and extensive synechiae in only 2, or 3.0 per cent. In general the synechiae are found relatively late in the disease. Fig. 1 shows an angle open with no synechiae. Fig. 2 shows an angle with the filtration area completely covered by synechiae. Out of 21 cases of chronic congestive glaucoma (Table II) synechiae were to-

TABLE I.

NON-CONGESTIVE GLAUCOMA (66 Unoperated Cases)

NO ANTERIOR PERIPHERAL SYNECHIAE	49	74.3%
MINOR ANTERIOR PERIPHERAL SYNECHIAE	15	22.7%
EXTENSIVE ANTERIOR PERIPHERAL SYNECHIAE	2	3.0%

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6-10, 1940, Cleveland, Ohio.

Wilmer Ophthalmological Institute of Johns Hopkins Hospital and University.

TABLE II.

CHRONIC CONGESTIVE GLAUCOMA (21 Unoperated Cases)

NO ANTERIOR PERIPHERAL SYNECHIAE	4	19.0%
MINOR ANTERIOR PERIPHERAL SYNECHIAE	6	28.6%
EXTENSIVE ANTERIOR PERIPHERAL SYNECHIAE	11	52.4%

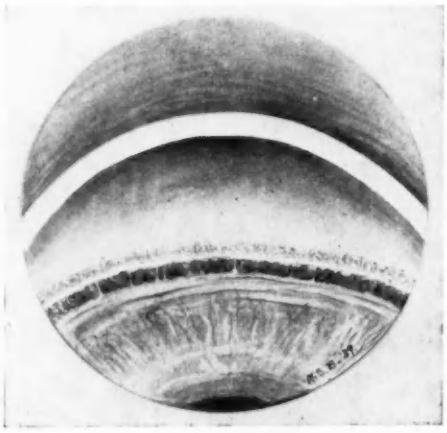


FIG. 1 — Open angle with no peripheral synechiae.

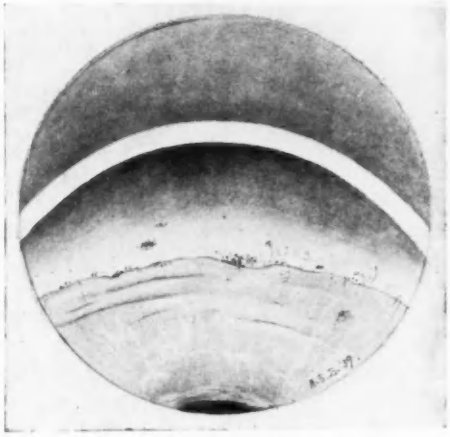


FIG. 2 — Angle completely closed with anterior peripheral synechiae.

tally absent in 4 cases, or 19 per cent (all of them early cases with few congestive attacks), minor synechiae were found in 6, or 28.6 per cent, and extensive adhesions in 11, or 52.4 per cent. There were too few cases of acute congestive glaucoma which could be satisfactorily studied to permit statistical conclusions. Certainly in all, the iris was pressed up against the root of the cornea but it was not always easy to decide whether definite adhesions had formed.

Anterior peripheral synechiae, then, do develop in all forms of primary glaucoma, but always apparently as a result rather than a cause of the glaucomatous process. Without doubt the synechiae do add further obstruction to the normal drainage mechanism and contribute to the progress of the disease, but cannot be regarded as a primary factor.

Study of the corneoscleral trabeculae is somewhat disappointing. Sclerosis of its fibers has often been advanced as a probable primary factor, but such sclerosis is difficult to recognize gonioscopically, and I have never been able to satisfy myself as to its presence or absence in the living eye. Obstruction of these channels by pigment is likewise difficult to interpret. While Otto Barkan[1] has attempted to indicate such blockage as the etiological factor in non-congestive glaucoma, I have been unable to find a similar correlation. There are many normal eyes with much trabecular pigment but no suggestion of glaucoma, and many other eyes with extremely little pigment deposit but with advanced glaucoma. Other factors including age and possibly race seem to play a very important role in the pigment question. Sugar[9] has also been unable to correlate pigmentation of the trabeculae with primary glaucoma.

Gonioscopic study of eyes in which glaucoma develops after cataract extraction reveals certain interesting features.

If there has been a severe postoperative uveitis, the appearance of the angle is not unlike that which is present in any type of secondary glaucoma. The filtration area is more or less completely obstructed by inflammatory debris. After an apparently uncomplicated extracapsular extraction, there may be enough lens debris accumulated in the filtration area to account for failure of the pressure regulating mechanism. This picture is an exaggeration of that seen in glaucoma capsulare. When glaucoma develops after an uneventful intracapsular extraction (a rare occurrence) in an eye which has had no previous evidence of glaucoma and of which the gonioscopic picture was normal before operation, there is always a record of delayed reformation of the anterior chamber and detachment of the choroid. Examination of the angle shows formation of extensive anterior peripheral synechiae, obviously occurring during the period when the surgically traumatized iris was in intimate contact with the anterior structures of the chamber. Similar adhesions may also follow extracapsular extraction. Preoperative and postoperative study of many eyes in which uncomplicated cataract extractions have been performed shows that these synechiae occur only when there has been some delay in reformation of the chamber. As a means of preventing this complication, air injection into the anterior chamber at the end of extraction, as suggested by Burch[4] and others, might be considered. It is questionable, however, whether such an additional maneuver at the time of cataract operation is advisable. Synechiae do not always form when the chamber is flat and, even when they do, are not often extensive enough to cause later trouble. A similar prophylactic step is the use of an adequate corneoscleral suture[7] which will markedly decrease the incidence of delayed reformation of the chamber.

Gonioscopic investigation of the results of glaucoma surgery is particularly instructive in two regards. From an investigative standpoint, it brings to light some of the causes of failure not otherwise suspected. From the individual surgeon's point of view, it is useful in giving him a more complete realization of exactly what he has accomplished and where his incisions have gone.

After cyclodialysis, the findings are simple. The operative cleft either remains open to a greater or lesser extent or it becomes closed. Almost without exception, when the greater portion of the cleft remains patent, the tension is controlled (Fig 3). When it becomes

FIG. 3 — Open cyclodialysis.

completely or nearly completely closed the operation fails. Otto Barkan[2] has reported similar observations. In some eyes, repeated gonioscopic examinations show the opening becoming less and less, and as it closes, coincident examination of tension, vision, and fields show that the glaucoma is slipping out of control. An unsuccessful cyclodialysis usually closes with extremely dense, solid synechiae which completely obliterate the normal structures in that portion of the angle and leave the eye in worse condi-

tion than it was before operation. There are two obvious factors which predispose to early closure. One is an extremely narrow angle where there is an obvious tendency for the edges of the opening to fall together again. The other is clogging of the opening by blood from anterior chamber hemorrhage. In many instances, instead of becoming absorbed, the remains of the hemorrhage in the anterior chamber tend to become organized and promote healing rather than patency of the internal wound. The obvious remedy for this situation is to follow Gradle's[5] advice to perform cyclodialysis in the upper quadrants and keep the patient's head well elevated after operation.

Cyclodialysis, as applied to ordinary cases of glaucoma, generally has been less satisfactory than the external filtering operations. The shallower the chamber the more likely is the opening to close. Thus the aphakic eye would seem to provide ideal conditions for cyclodialysis for here there is the least tendency for the iris to be pushed up into the angle once it is separated. Experience has shown this to be the case, and cyclodialysis seems to be the best operation for aphakic glaucoma.

In order to lessen the likelihood of closure of cyclodialysis openings the procedure of combining iridectomy with the cyclodialysis, as suggested by Wooten[15] and advocated by Wheeler,[14] is logical. I have not had enough experience with this method to present statistical conclusions, but I do know that it is not a panacea for I have seen cyclodialysis close over the area where all iris tissue has been removed.

Study of iris inclusion operations has been confined to two types of iridencleisis. One is the classical "iridencleisis cum iridotomia meridionali" of Holth in which the iris is withdrawn under a conjunctival flap and a meridional iridotomy performed leaving both pillars incarcerated. The other is a slight modification in which, after the radial iridotomy is made, each pillar is seized successively, torn loose at its root, and incarcerated towards the corner of the incision. This procedure results in two separated filtering wicks of iris with a moderate basal coloboma between them (Fig. 4). A

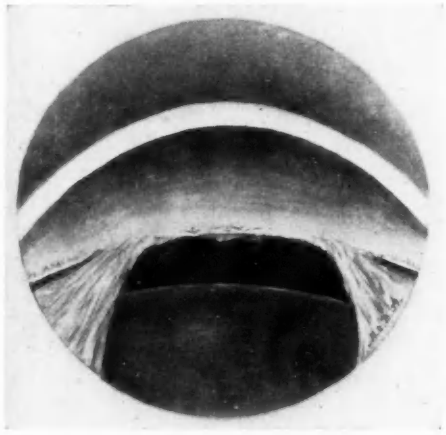


FIG. 4 — Iridencleisis.

somewhat larger original keratome incision is required. The second method is particularly applicable during subacute or acute congestive attacks in a chronically glaucomatous eye where iridectomy might be the operation of immediate choice, but provides inadequate permanent drainage.

Comparison of gonioscopic examinations before and after iridencleisis shows one outstanding feature which must be regarded as the direct result of surgical intervention. In many cases where there were no anterior peripheral synechiae before operation, they were present postoperatively. Where synechiae were present preoperatively, they often were increased postoperatively. Some were adhesions to corneoscleral trabeculae only, some were adhesions to the anterior annular ring completely obscuring the trabeculae, and some were combina-

tions of the two. In most instances there were adhesions of the pillars of the iris in the immediate vicinity of their inclusion. Such adhesions were recognized by Werner,[13] but their importance was not pointed out.

The effect of this additional formation of synechiae is not always immediately obvious. However, a statistical study of cases adequately followed over a period of from six months to three years after operation indicates that they are of some importance. It would seem reasonable to suppose that this additional embarrassment of the normal filtration mechanism might well be enough added load to influence the outcome in border-line cases. Such proves to be the case. Where the filtering operation affords sufficient drainage to relieve the original glaucoma plus any additional load imposed by synechiae, all is well. Where the filtering operation is barely sufficient to handle the original load, further embarrassment by formation of postoperative synechiae may turn the tide unfavorably. It is well recognized that surgery has a higher record of success in the non-congestive (deep chamber) type of glaucoma than in the chronic congestive (shallow chamber) type. The preoperative presence or absence of synechiae is probably an important factor and somewhat analogous to the effect of synechiae produced by an operation. Table III shows the effect on the end results of anterior peripheral synechiae formed after operation. Only cases with no other apparent source of failure are included.

The terms used to describe surgical results are as follows: If an operation alone results in complete control of the glaucoma, with no further rise in tension, loss of vision, or decrease in field, it is termed a "full success." If postoperative miotics are required to fulfill these criteria, the operation is termed a "partial success." If there is postoperative rise in tension, loss of vision, or loss of field, the operation is classed as a "failure." All of the cases included in this study have been followed regularly in a special "glaucoma clinic" where careful periodic examinations have been made. The correlation between poor re-

TABLE III.
IRIDENCLEISIS IN CHRONIC GLAUCOMA

ANGLE BEFORE OPERATION	ANGLE AFTER OPERATION	RESULT
NO SYNECHIAE....43	NO SYNECHIAE....15	FULL SUCCESS....13
		PARTIAL SUCCESS....2
		FAILURE....0
	FEW ANTERIOR PERIPHERAL SYNECHIAE....18	FULL SUCCESS....10
		PARTIAL SUCCESS....7
		FAILURE....1
	EXTENSIVE ANTERIOR PERIPHERAL SYNECHIAE....10	FULL SUCCESS....1
		PARTIAL SUCCESS....5
		FAILURE....4
SYNECHIAE PRESENT....11	UNCHANGED....7	FULL SUCCESS....2
		PARTIAL SUCCESS....2
		FAILURE....3
	SYNECHIAE INCREASED....4	FULL SUCCESS....0
		PARTIAL SUCCESS....2
		FAILURE....2

sults and formation or increase of synechiae is at once apparent.

To test out the hypothesis that these synechiae were caused by collapse of the anterior chamber during the presence of the inevitable slight postoperative irritation, I attempted, in a small series of cases, to keep the iris away from the cornea by refilling the anterior chamber with salt solution at the end of operation. This maneouver was not uniformly successful, for the anterior chamber had frequently disappeared by the next day. In another small series, air was used with much greater success. Out of seven cases, air remained in the chamber in six, being slowly absorbed and replaced by aqueous. In none of these six was the chamber ever flat, in none did any synechiae form, and in all the glaucoma has been controlled completely ever since (18-23 months). MacMillan[6] since has recommended air under the conjunctival flap in trephine operations as a worth while procedure. Apparently by this method a certain amount of air was also introduced into the anterior chamber and it is possible that this may have played some part in his success.

Whether or not prophylactic air injection into the anterior chamber is sufficiently important to justify further complication of the surgical technique is a debatable point. During the past year I have adopted a different routine. The operation is performed in the usual manner. If the anterior chamber fails to reform promptly after operation, it is then inflated with air through a small sharp hypodermic needle. Any difficulty in introducing a needle at the limbus at this time may be obviated by forming a track for it with a narrow, sharp Ziegler knife. The use of salt solution to fill out a long collapsed chamber has been suggested before,[3] but, for early cases, air seems to be superior.

In two cases an attempt was made to loosen preexisting synechiae. After keratome incision, the iris was grasped with forceps and pulled to and fro in an exaggeration of the manner in which intracapsular cataract forceps were used. Then the inclusion was performed and the chamber was filled with air. After operation, many of the adhesions were found to have been broken and their reestablishment was prevented by the air injection. While of some interest from the experimental point of view, this procedure is not to be recommended for general clinical use. The additional trauma to iris tissue is not desirable and there is no evidence to indicate that function will be resumed at the site of former adhensions.

The gonioscope reveals several interesting complications after corneoscleral trephining (Fig. 5). One of them is the

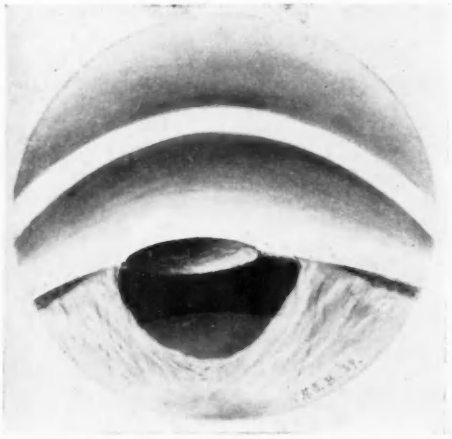


FIG. 5 — Corneoscleral trephining.

same formation of anterior peripheral synechiae seen following iris inclusion operations. The incidence is somewhat lower with trephining, but the end results are similar. Table IV excludes all cases where other complications were encountered. Again, the parallelism between synechiae and poor results can be

TABLE IV.
CORNEOSCLERAL TREPHINING IN CHRONIC GLAUCOMA

ANGLE BEFORE OPERATION		ANGLE AFTER OPERATION		RESULT	
NO SYNECHIAE	10	NO SYNECHIAE	4	FULL SUCCESS	4
				PARTIAL SUCCESS	0
				FAILURE	0
		FEW ANTERIOR PERIPHERAL SYNECHIAE	4	FULL SUCCESS	1
				PARTIAL SUCCESS	3
				FAILURE	0
		EXTENSIVE ANTERIOR PERIPHERAL SYNECHIAE	2	FULL SUCCESS	0
				PERTIAL SUCCESS	0
				FAILURE	2
SYNECHIAE PRESENT	4	UNCHANGED	2	FULL SUCCESS	1
				PARTIAL SUCCESS	0
				FAILURE	1
		SYNECHIAE INCREASED	2	FULL SUCCESS	0
				PARTIAL SUCCESS	1
				FAILURE	1

seen at once. Another very important finding is anterior prolapse of ciliary processes into the trephine hole (Fig. 6). This complication has been described by Reese[8] and Troncoso.[11] In some instances this prolapse may be the source of constant mechanical irritation and is probably the cause of the unexplained "quite iridocyclitis" of trephining. In more severe prolapse, the ciliary tissue may plug the hole completely (Figs. 7 and 8) or may throw out so much scar tissue that drainage is entirely ob-

FIG. 6 — Photograph of ciliary processses in trephine opening.

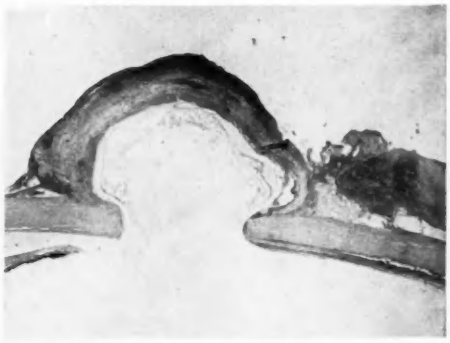


FIG. 7 — Histological section of trephine bleb lined with ciliary tissue.

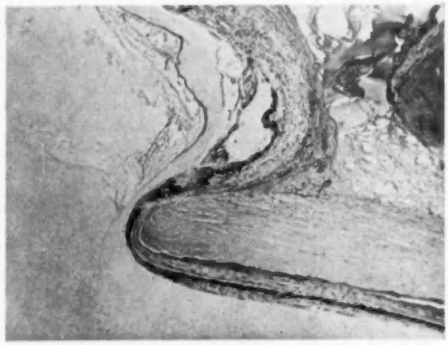


FIG. 8 — Detail of ciliary tissue in trephine opening.

structed. The deeper the angle and the further forward the trephining is performed, the less likely are these ciliary incarcerations to occur. Early restoration of the anterior chamber does not appear to be as important a factor in preventing these ciliary complications as it does in avoiding the increase of trabecular synechiae. Apparently the two most important features are proper forward location of the trephine opening and substitution of some other operation in eyes with marked advance of the lens-iris diaphragm. In one instance I have observed prolapse of the edge of the lens into a trephine opening. This very efficient plug thoroughly defeated the purpose of the trephining, but, interestingly enough, it did not cause cataract formation in the ensuing two years of observation.

SUMMARY

This study confirms the opinion of other gonioscopists about the role of synechiae in the development of glaucoma. Preoperative and postoperative examinations show the part played by synechiae in causing glaucoma after cataract operations. The relationship of patency of a cyclodialysis opening to control of tension is illustrated. Importance of anterior peripheral synechiae in external filtration operations is pointed out, and other factors in efficiency of corneoscleral trephining are discussed.

REFERENCES

1. Barkan, Otto: Glaucoma: Classification, causes, and surgical control; results of microgonioscopic research, Am. J. Ophth. 21:1099 (Oct.) 1938.
2. Barkan, Otto: New operation for chronic glaucoma; restoration of physiological function by opening Schlemm's canal under direct magnified vision, Am. J. Ophth. 19:951 (Nov.) 1936.
3. Black, G. W.: Glaucoma, Trans. Ophth. Soc. United King. 55:571, 1935.
4. Burch, F.: Personal communication.
5. Gradle, H. S.: Personal communication. Also cited by Sugar, Am. J. Ophth. 23:853 (Aug.) 1940.
6. MacMillan, J. A.: Air injection as a factor in maintaining filtration following corneoscleral trephining in glaucoma, Trans. Am. Ophth. Soc. 37:127, 1939.
7. McLean, J. M.: New corneoscleral suture, Arch. Ophth. 23:554 (March) 1940.
8. Reese, A. B.: Ciliary processes; their relation to intra-ocular surgery, Am. J. Ophth. 17:422 (May) 1934.
9. Sugar, H. S.: Concerning chamber angles; gonioscopy, Am. J. Ophth. 23:853 (Aug.) 1940.
10. Thorburn, A.: Thesis, Stockholm, 1927.
11. Troncoso, M. U., and Reese, A. B.: Gonioscopic findings after Elliot operation, Trans. Ophth. Soc. United King. 53:366, 1933.
12. Troncoso, M. U.: Closure of angle of anterior chamber in glaucoma; its bearing on operation for relief of hypertension, Arch. Ophth. 14:557 (Oct.) 1935.
13. Werner, S.: Gonioscopical studies of operated cases of glaucoma, Acta Ophth. 10:112, 1932.
14. Wheeler, J. M.: Iridectomy with cyclodialysis for reduction of ocular tension, Arch. Ophth. 16:569 (Oct.) 1936.
15. Wootton, H. W.: Cyclodialysis combined with iridectomy in glaucoma simplex; preliminary report, Trans. Am. Ophth. Soc. 30:64, 1932.

THE RELATION OF THE GONIOSCOPIC FINDINGS TO THE INCIDENCE OF SECONDARY GLAUCOMA IN OPERATIVE APHAKIA

PETER C. KRONFELD, M.D.
and
E. E. GROSSMAN, M.D.
BY INVITATION
CHICAGO

THIS study concerns itself with states of persistently elevated intra-ocular tension in aphakic eyes in which

(1) careful examination before cataract extraction, including at least one tonometric reading, had revealed no sign of glaucoma;

(2) the inflammatory postoperative reaction was slight and had either completely subsided or was definitely diminishing in intensity 14 days after the operation;

(3) large intra-ocular hemorrhage had not occurred during operation or convalescence;

(4) there was no clinical sign of invasion of the anterior chamber by surface epithelium.

In the majority of the cases to which we refer, the glaucoma was recognized shortly after the cataract incision had healed water-tightly. Thus it seemed justifiable to consider these as cases of secondary glaucoma following cataract extraction.

Extensive discussions of this type of secondary glaucoma can be found in the older textbooks on ophthalmic surgery. Czermak and Elschnig[2] consider as "the most important factor in the pathogenesis of this form of glaucoma delayed closure of the wound entailing prolonged absence of the anterior chamber. During this period the touching surfaces — iris, and trabeculum sclerocorneale—are glued together. Pathologically, the iris is found adherent to the periphery of the cornea, the original chamber angle having become obliterated. The delayed closure of the wound is caused by incarceration between the wound lips of iris, lens capsule, or vitreous, or by other factors." Probably because this form of secondary glaucoma has become uncommon, references to it are scarce in the more recent treatises on ophthalmic surgery. Fox[3] reports "slow healing of the wound" in only one of 31 cases of postoperative glaucoma, that is, glaucoma observed after cataract extractions or discissions. As causes of glaucoma in his series, he lists "thick secondary cataract, lens material in the anterior chamber, vitreous in the anterior chamber, incarcerated iris, capsular tags in wound, previous glaucoma, atropine, and trauma to head," but does not mention delayed closure of the wound. Alvis[1] states that "great care in freeing the wound of all debris of capsule, iris, cortex, and clots, in order to secure quick and accurate wound closure, is entirely worth while," but he does not report a case of delayed closure of the wound in his small series of cases of glaucoma following cataract extraction.

The advent of gonioscopy revived the concept of a causal relationship between delayed closure of the wound, peripheral

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6-10, 1940, Cleveland, Ohio.

The Illinois Eye and Ear Infirmary, H. S. Gradle, M.D., Director.

TABLE I.

HOSPITAL NUMBER	OPERATION	RESTORATION TIME OF ANTERIOR CHAMBER IN DAYS	OTHER POST-OPERATIVE COMPLICATIONS	PERIOD BETWEEN CATARACT EXTRACTION AND RECOGNITION OF GLAUCOMA	GONIOSCOPIC FINDINGS AT THE TIME OF RECOGNITION OF GLAUCOMA	COURSE OF GLAUCOMA
17654 LE	Extracapsular, loop extraction, loss of vitreous.	30 days.	None.	3 months.	Angle closed.	Controlled by corneoscleral trephine.
19987 RE	Corneoscleral suture, intracapsular.	13 days.	None.	1 month.	Angle closed.	Controlled by 1 cyclodialysis.
19033 LE	Extracapsular, leaving much cortex behind iris.	13 days.	None.	1 month.	Angle closed.	Controlled by miotics.
20908 RE	Extracapsular; needling 2 mos. later.	12 days.	None.	7 months.	Angle closed.	Controlled by 1 cyclodialysis plus miotics.
LE	Unknown.	Unknown.	Unknown.	3 years.	Angle closed.	Far advanced, controlled by miotics after 1 cyclodialysis and 1 trephine.
20319 LE	Corneoscleral suture, intracapsular.	12 days.	None.	1 month.	Angle closed except from 5 to 7 o'clock.	Controlled by miotics.
20330 RE	Extracapsular.	10 days.	None.	1 month.	Angle closed.	Controlled by cyclodialysis.
19165 RE	Extracapsular.	10 days.	None.	1 month.	Angle closed.	Controlled by cyclodialysis.
18162 RE	Intracapsular.	9 days.	None.	16 months.	Angle closed except from 5 to 7 o'clock.	Very mild, controlled by miotics.
16577 LE	Corneoscleral suture, extracapsular.	7 days.	Iris prolapse, repair	1 month.	Angle closed.	
21614 RE	Extracapsular.	7 days.	None.	5 months.	Angle closed.	Uncontrolled by miotics.
18522 LE	Attempted intracapsular.	7 days.	None.	3 weeks.	Angle closed.	Controlled by miotics.
16110 LE	Attempted intracapsular.	6 days.	None.	8 months.	Angle closed.	Controlled after 2 cyclodialysis.
20808 RE	Intracapsular.	7 days.	None.	7 months.	Angle closed.	Controlled by 1 cyclodialysis.
13970 RE	Intracapsular, round pupil.	6 days.	None.	18 months.	Angle closed.	Far advanced, controlled by 1 cyclodialysis.
LE	Unknown.	Unknown.	Unknown.	Unknown.	Angle closed except small areas at 4 and 8 o'clock.	Uncontrolled by miotics, operation advised.
19470 RE	Extracapsular.	5 days.	None.	7 months.	Angle closed.	Very mild, controlled by 1 cyclodialysis.
LE	Extracapsular.	5 days.	None.	1 month.	Angle closed.	Controlled by 1 cyclodialysis.
17083 RE	Attempted intracapsular, leaving much cortex behind the iris.	4 days.	None.	1 month.	Angle closed.	Controlled after 3 cyclodialyses, 1 trephine and 1 cyclodiathermy.
17096 RE	Attempted intracapsular, loop extraction, vitreous loss.	3 days.	None.	6 months.	Angle closed except 5:30 to 6:30 where trabecular adhesions are present.	Very mild, controlled by miotics.

TABLE I.—Continued

HOSPITAL NUMBER	OPERATION	RESTORATION TIME OF ANTERIOR CHAMBER IN DAYS	OTHER POST-OPERATIVE COMPLICATIONS	PERIOD BETWEEN CATARACT EXTRACTION AND RECOGNITION OF GLAUCOMA	GONIOSCOPIC FINDINGS AT THE TIME OF RECOGNITION OF GLAUCOMA	COURSE OF GLAUCOMA
14787 RE	Intracapsular.	3 days.	Choroidal detachment noted on 10th post-operative day.	2 months.	Angle closed.	Controlled by cyclodialysis plus miotics.
17742 RE	Extracapsular.	4 days.	Fresh hemorrhage into AC on 6th postoperative day.	3 months.	Dense trabecular adhesions, obliterated in parts above.	Controlled by cyclodialysis.
19178 LE	Extracapsular, leaving much cortex behind the iris.	2 days.	None.	1 month.	Angle closed.	Controlled by cyclodialysis.
19113 RE	Extracapsular.	4 days.	Fresh hemorrhage into AC on 5th postoperative day.	3 months.	Angle closed except two rather broad areas at 5 and 7 o'clock.	Controlled by miotics.
17066 LE	Extracapsular.	4 days.	Small hemorrhage into AC on 4th postoperative day.	2 months.	Angle closed.	Controlled by miotics.
20388 RE	Attempted intracapsular.	Unknown.	Unknown.	1 month.	Angle closed.	Controlled by 1 cyclodialysis plus miotics.
18018 RE	Extracapsular.	Unknown.	Rupture of wound on 4th postoperative day.	1 month.	Angle closed except at 12:30 and 6:00 o'clock.	Controlled by miotics.
20879 LE	Extracapsular, leaving much cortex behind the iris; 2 needlings.	Unknown.	Unknown.	20 months.	Angle closed.	Far advanced, controlled by cyclodialysis.
20247 RE	Attempted intracapsular, loop extraction, loss of vitreous.	4 days.	None.	2½ years.	Open angle.	Controlled by miotics.
20924 RE	Attempted intracapsular, leaving much cortex behind the iris.	1 day.	Hemorrhage into AC on 4th postoperative day.	3½ years.	Open angle.	Far advanced, controlled by cyclodialysis plus miotics.
G40-686 LE	Extracapsular, leaving much cortex behind the iris.	1 day.	None.	1 month.	Open angle, pigmentation of trabeculum.	Uncontrolled at present.
19856 RE	Extracapsular, loop extraction, leaving much cortex behind the iris, loss of vitreous; needling 3 months after cataract extraction.	2 days.	None.	6 months.	Upper third obliterated by lens cortex, lower two-thirds open except for a few tent-shaped trabecular adhesions.	Uncontrolled by several operations.

anterior synechiae, and secondary glaucoma. In his paper entitled "Concerning the Chamber Angle," H. S. Sugar[4] refers to "a series of 30 eyes with secondary glaucoma following extraction, in 29 of which the chamber angle was completely obliterated. Many of the histories indicated a prolonged postoperative period during which the chamber was collapsed, associated in some instances with recognized choroidal detachment or iris prolapse. Complete obliteration of the angle is probably the cause of this type of glaucoma."

Our study was undertaken to define more closely the relationship between the following three factors:

Delayed restoration of the anterior chamber (DR).
The formation of peripheral anterior synechiae (PS).
The occurrence of glaucoma (SG).

Table 1 contains all those cases of secondary glaucoma following cataract extraction which are on record in the glaucoma clinic of the Illinois Eye and Ear Infirmary and in which the four conditions stated in the introduction (series A) are represented. In most instances the hospital records indicated clearly the number of days required for restoration of the chamber. In some cases restoration of the chamber probably was more delayed than indicated in the table (patient 14787). Unless stated otherwise, there was no visible incarceration of any intra-ocular tissue between the lips of the wound. There may have been a microscopic incarceration of intraocular tissues or the DR may have been caused by other factors. In its earlier stages the glaucoma usually caused no subjective symptoms, being characterized by an insidious, completely compensated course. Usually its presence was recognized accidentally during a routine follow-up consultation. In 19 of the 32 eyes listed in Table 1, the SG was recognized within five months following the cataract extraction. The 11 patients in whom the glaucoma was recognized later did not present themselves for follow-up examination in the interim. In three of these cases the glaucoma took a mild course which would indicate why the patients did not return to the clinic sooner. Among the cases of SG, in which the diagnosis was made in its later stages, there were four cases in which, at the time of recognition of the SG, very extensive field defects were discovered, indicating a glaucomatous state of long standing. Thus, it appears highly probable that in the large majority of the cases listed in Table 1, the onset of the SG occurred within a few months after the cataract extraction.

The gonioscopic examinations referred to in Table 1 were made by the physician in charge of the glaucoma clinic. The term "angle closed" implies iris adhesions to the corneoscleral trabeculum throughout its entire circumference, the apex of the new chamber angle lying at or slightly behind the end of Descemet's membrane, or, in gonioscopic terminology, the line of Schwalbe. The term "trabecular adhesions" is used here in the same sense as originally proposed by Troncoso,[5] that is, for peripheral anterior adhesions of such meridional extent that the apex of the new angle lay in the region of the posterior third of the trabeculum.

Of the 32 eyes listed in Table 1, 28 showed gonioscopically extensive peripheral anterior adhesions, whereas in four eyes the angle was open. This difference in the gonioscopic picture could not have been due to a phase difference because in 12 eyes the closed angle was discovered one month after the cataract extraction, that is, in a very early phase of the glaucoma. In two of the cases with open angle, on the other hand, this gonioscopic observation was made 2½ and 3½ years after the cataract extraction.

Table 1 thus seems to contain two types of cases, namely, early glaucoma with closed angles and far advanced glaucomas with open angles. These gonioscopic findings strongly suggest heterogeneity of this series of cases with regard to the pathogenesis of the glaucoma.

In 17 cases the delayed restoration of the anterior chamber was the only postoperative complication noted on the patient's chart. In the remaining 15 cases the following complications occurred: Loss of vitreous, retention of much lens cortex, late ruptures of the wound, iris prolapse, and hemorrhage into the anterior chamber. It is generally conceded that each of these complications, occurring singly or combined with other factors, may contribute to the development of secondary glaucoma. As figure 1 shows, these complications occurred with greater relative frequency in the cases with slight DR. On the other hand, in the cases with marked DR, complications other than DR were relatively rare. Thus, in the cases with short DR, it appears that several potential pressure-disturbing complications had occurred; whereas in the cases with marked DR, the DR was the outstanding and perhaps the only significant pressure-disturbing factor.

We are concerned here with only the cases of SG following cataract extraction where extensive peripheral anterior synechiae has occurred. These synechiae, as previously stated, were discovered at such an early date after the cataract extraction as to render very probable the interpretation by the earlier authors that the adhesions antedated and were a causative factor in the development of the SG. In line with this interpretation a detailed study was made of the effect of cataract extraction upon the anatomical relationship between the ciliary portion of the iris and the lateral wall of the angle. As a first step, 50 aphakic eyes (series B) upon which a successful cataract extraction had been performed at least eight months prior to the gonioscopic examination, and which were free of signs of any form of glaucoma or of uveitis, were examined with the gonioscope. In the area of the incision the gonioscope in almost every case revealed abnormal conditions. In most cases a "total" iridectomy had been performed producing an iris stump which had become adherent to the trabeculum. The pillars of the coloboma without excep-

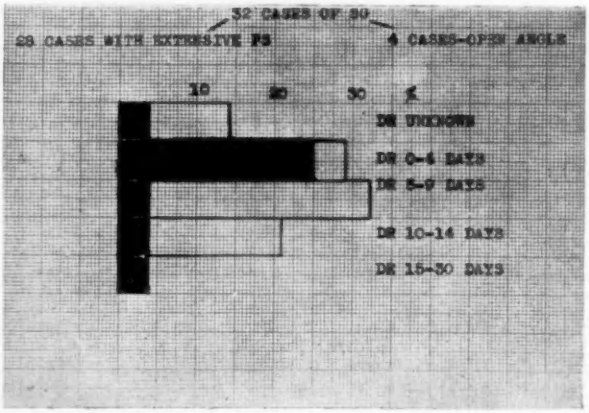


FIG. 1 — The shaded areas in the diagram indicate those cases with SG in which other complications had occurred in addition to the DR.

tion had formed anterior adhesions of varying meridional extent (Fig. 2). Thus, the chamber angle in the area of the incision had become more or less completely obliterated. In the remainder of the chamber angle, circumscribed adhesions between the iris and the most posterior portions of the trabeculum were found in almost every case. The extent of these adhesions in circumferential direction varied from thin iris strands, which at first glance could have

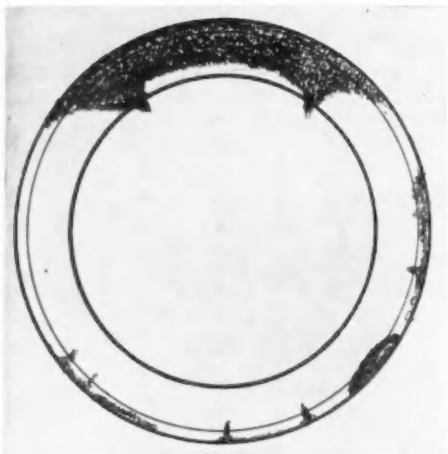


FIG. 2.—Graphic record of the extent of the peripheral anterior synechiae (shaded area) which were found in most of the patients of series B. The three circles represent, from without in, the apex of the angle, the anterior border of the ciliary body, and the line of Schwalbe.

been mistaken for physiological iris processes, to tent-shaped elevations of the iris stroma, the apex of which adhered to the trabeculum. The latter type of adhesion extended in some cases over one or more hours of the clock. The characteristic feature of all of these adhesions, which in no appreciable way interfered with the maintenance of normal intra-ocular pressure, was their very limited extent in meridional direction, the iris adhesions seldom ever covering more than the posterior fourth of the distance between the anterior border of the ciliary body and the line of Schwalbe. This gonioscopic picture is consistent with that seen after other intra-ocular operations followed by prompt restoration of the anterior chamber.

A study of the hospital records of 120 unselected cataract extractions performed between February and July, 1940, revealed DR of more than three days in 20 instances (16.7%) and of more than five days in 11 instances (9.2%). Of these 20 cases with DR, 13 of the patients presented themselves for re-examination (series C, table 2). In the cases of DR of less than five days, the gonioscopic examination disclosed adhesions of the type found in series B. In circumferential direction the extent of the PS varied considerably, whereas in meridional direction the PS was confined to the posterior one-fourth of the area located between the anterior border of the ciliary body and the line of Schwalbe. Without exception, the presence of such adhesions was found to be compatible with a normal or low intra-ocular tension. In two of these cases the period of postoperative observation was seven months and in two, it was five months. The conclusion may be justifiable that, as a rule, a DR of less than five days and the PS entailed by such a DR are, in the absence of other pressure-raising factors, not followed by an increase in intra-ocular tension and should therefore not be considered serious complications.

In the cases with DR of more than five days, gonioscopic examination revealed PS which were definitely more extensive than those found in the cases of DR of less than five days. These PS are recorded graphically in figure 3 in the form of drawings of the anterior wall of the anterior chamber as seen from behind.

The gonioscope revealed three variations of the anterior edge of the adhesions, namely: a solid, sharply demar-

TABLE II.

HOSPITAL NUMBER	DATE OF CATARACT EXTRACTION	OPERATION	RESTORATION TIME OF ANTERIOR CHAMBER IN DAYS	OTHER POSTOPERATIVE COMPLICATIONS	GONIOSCOPIC FINDINGS	TENSION
19871 RE	2-17-40.	Intracapsular.	4 days.	Marked chemosis for 10 days.	Heavy trabecular pigmentation, no adhesions except in area of incision.	8-27: 24. 9-3: 24.
20420 RE	4-18-40.	Extracapsular.	4 days.	None.	No adhesions except in area of incision.	8-27: 20. 9-3: 19.
20331 RE	4-10-40.	Extracapsular.	4 days.	None.	Annular adhesion to the posterior 1/5th of the trabeculum.	8-27: 17. 9-3: 15.
20817 RE	6-25-40.	Intracapsular.	6 days.	None.	Several tent-shaped adhesions to the posterior 1/5th of the trabeculum.	Several tensions of 15 during August and September, 1940.
19872 LE	2-16-40.	Intracapsular.	4 days.	Small vitreous prolapse noted on 7th postoperative day, treated with trichloracetic acid.	Fig. 1.	9-10: 21. 9-17: 23.
20470 LE	4-30-40.	Extracapsular.	6 days.	None.	Fig. 2.	9-10: 18. 9-17: 16.
21097 RE	7-5-40.	Extracapsular.	7 days.	None. (cystic scar).	Fig. 3.	9-10: 18. 9-17: 18.
20970 LE	7-11-40.	Extracapsular, leaving much cortex behind iris.	10 days.	None.	Fig. 4.	9-3: 15. 9-10: 13. 9-17: 15.
20708 RE	5-16-40.	Intracapsular.	15 days.	None.	Fig. 5.	9-3: 15. 9-10: 17.
20264 LE	4-17-40.	Extracapsular.	12 days.	None.	Fig. 7.	9-10 to 9-18 daily tensions varied from 23 to 29.
20679 RE	5-14-40.	Extracapsular.	7 days.	None.	Fig. 6.	9-5: 32. 9-10: 24. 9-17: 24.
20023 LE	4-24-20.	Extracapsular.	10 days.	None.	Fig. 8.	9-3: 28. 9-12: 2 p.m.: 37. 5 p.m.: 37.
21011 RE	6-18-40.	Intracapsular, small loss of vitreous.	10-12 days.	None.	Fig. 9.	7-12: 18. 8-10: 15. 8-24: 18. 8-31: 24. 9-3: 28. 9-10: 43. 9-12: 40.

cated line, a fuzzy, scalloped zone, and multiple, isolated iris strands. The condition of the anterior border layer of the iris seemed to determine the type of edge present. The dense border layer without crypts, such as is found in most dark brown eyes, tended to give rise to adhesions with solid line edges. On the other hand, in the case of a delicate blue or grey iris, the synechiae formed were usually characterized by fuzzy edges. From these observations it appears possible that the condition of the anterior border layer of the iris is a factor determining also the density and perhaps even the extent of the PS. Within the group of DR of more than five days there was no apparent parallelism between the DR and the extent of the PS. Repeated examinations did not reveal a change in the extent of the PS over periods up to three months. In the course of these repeated examinations we were able actually to observe the development of glaucoma in those two eyes in which the PS were most extensive (20023, 21011). Two more eyes are at present in a border-line condition (20264, 20679) and will, like the rest of the cases, be watched closely. Through a continuation of this work it may be possible to define more closely the extent of postoperative PS which entails the danger of subsequent glaucoma.

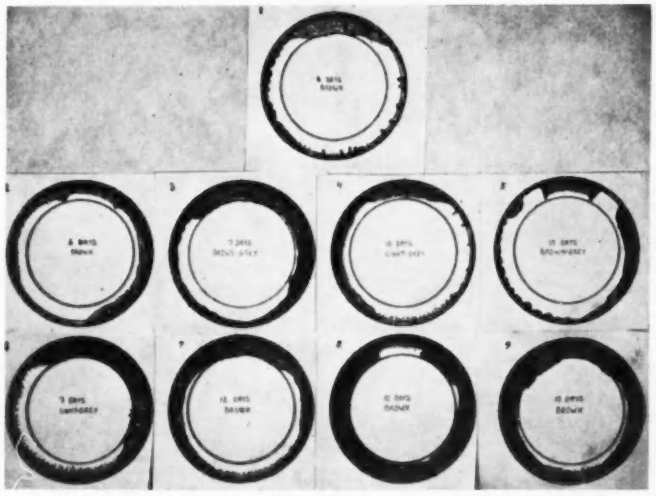


FIG. 3 — Graphic record of the peripheral anterior synechiae (shaded area) found in those patients of group C in which DR was marked. The three circles represent, from without in, the apex of the angle, the anterior border of the ciliary body, and the line of Schwalbe.

SUMMARY

This study deals with the well-known form of persistent secondary glaucoma occurring in operative aphakia in which there was delayed healing of the incision. During the era before the gonioscope was devised, the mechanism of this form of glaucoma was explained as that of chamber angle obliteration produced by adhesions between the iris and the lateral wall of the angle occurring during the period of absence of the chamber. Gonioscopic evidence is presented indicating that delayed closure of an operative incision actually leads to

formation of peripheral anterior synechiae of an extent depending upon the length of the delay, and perhaps also upon the texture of the anterior border layer of the iris. The occurrence of glaucoma in such cases is shown to depend upon and to be secondary to the presence of extensive peripheral anterior synechiae. Gonioscopic examination following cataract extraction promises to afford a means of foretelling derangements of the intraocular pressure.

REFERENCES

1. Alvis, B. Y.: Management of glaucoma following cataract operation, Am. J. Ophth. 22:518 (May) 1939.
2. Czermak, W.: Die augenärztlichen Operationen, edited by A. Elschnig, 1. Bd. Berl. u. Wien, Urban and Schwarzenberg, 1907.
3. Fox, S. A.: Postoperative glaucoma, Arch. Ophth. 16:585 (Oct.) 1936.
4. Sugar, H. S.: Concerning chamber angle; gonioscopy, Am. J. Ophth. 23:853 (Aug.) 1940.
5. Troncoso, M. U.: Gonioscopy and its clinical applications, Am. J. Ophth. 8:433 (June) 1925.

DISCUSSION

RAMÓN CASTROVIEJO, M.D., New York, N. Y.: Doctors McLean, Kronfeld, and Grossmann deserve to be congratulated for their excellent papers.

I had the privilege of working with Doctor Troncoso in the study of the angle of the anterior chamber, both in animal and human eyes. Through Doctor Troncoso I became acquainted with the use of the gonioscope. I wish to give credit to Doctor Troncoso for all his teachings, and for the interest that he aroused in me for the study of this subject.

The conclusions drawn by Doctor McLean in his paper seem to be in agreement with the conclusions obtained by Doctors Troncoso and Reese several years ago, after studying the same type of cases reported by Doctor McLean.

My limited experience on this subject shows similar findings.

Doctors Kronfeld and Grossmann have proved in their paper that late restoration of the anterior chamber after cataract extraction is one of the most frequent causes of anterior synechiae, with the subsequent development of secondary glaucoma. They state that late restoration of the anterior chamber is a frequent occurrence in their service, in spite of the use of corneoscleral sutures. In my experience, which includes over 150 cataract extractions in which a certain type of corneoscleral suture was used, late restoration of the anterior chamber (more than 48 hours) has been observed in only two cases, and in none of the cases have I observed the development of secondary glaucoma, perhaps because the anterior chamber was restored promptly after the operation. I believe corneoscleral sutures, when adequate, accelerate the progress of healing of the incision made for the extraction of cataracts, favoring an early restoration of the anterior chamber and preventing secondary glaucoma.

The average ophthalmologist nowadays is paying more attention than heretofore to the study of the angle of the anterior chamber. In a not distant future, the study of the angle of the anterior chamber will be as familiar to the ophthalmologist as the observation of the eye with the ophthalmoscope and the slit lamp.

The angle of the anterior chamber can be clearly visualized by means of the gonioscope of Doctor Troncoso and special contact glasses. The corneal microscope may be used also for the study of the angle, as I have demonstrated on several occasions. It is even possible nowadays, with special illumination and cameras adapted to the gonioscope or to the corneal microscope, to obtain black and white and colored photographs of normal and pathological aspects of the angle of the anterior chamber, as demonstrated by those which are presented in this discussion.

The importance of gonioscopy has been proved in the papers of Doctors Troncoso, Reese, Bruce, Barkan, Sugar, McLean, Kronfeld, Grossmann, myself, and others.

MANUEL URIBE TRONCOSO, M.D., New York, N. Y.: I wish to emphasize the importance of the paper by Doctors Kronfeld and Grossmann and its implications, not only from the standpoint of gonioscopy but also from that of physiopathology.

The authors limited their scope to the study of the relationship between delayed restoration of the anterior chamber after cataract extraction, the formation of peripheral synechiae, and the role of the latter in the occurrence of secondary glaucoma. Their material is abundant, and the conclusions at which they arrive are entirely sound.

As a first step, they examined 50 aphakic eyes upon which a successful cataract extraction had been performed and in which there had been no primitive or late signs of secondary glaucoma. In almost all of them gonioscopic examination revealed abnormal conditions at the site of the incision in the inner limbus. In most cases a "total" iridectomy had been performed, producing an iris stump at the base of the coloboma. This stump had become adherent to the trabeculum, and the pillars of the coloboma had become attached to the wound. Thus the chamber angle had become more or less obliterated. In the remaining parts of the angle they also found circumscribed adhesions between the iris and the trabeculum. However, the significant feature was that these limited peripheral synechiae did not interfere with the aqueous outflow, and the tension was normal.

I have observed and called attention several times to these complications. They usually remain entirely unknown to the surgeon who limits himself to the external aspect of his healed incision. The merit of this paper lies in the fact that a systematic study of these complications has been made in a great number of aphakic eyes.

The partial closure of the angle may have no effect on the intra-ocular tension for a while. However, after months or years, the factors of senility on vascular, nervous, and metabolic diseases may start to develop in a patient; and because of the favorable conditions in this area and the limited outflow from the chamber, may begin to produce symptoms of hypertension or glaucoma. When these complications produce a great encroachment on the angle, the patient should be kept under observation.

A careful study of 120 cases of cataract extractions has been made, and a delayed reformation of the anterior chamber in 32 eyes has been found. The authors believe that the delayed closure of the wound leads to peripheral synechiae, the extent depending upon the length of the delay. When this delay is less than six days, it is not usually followed by an increase of tension, although the authors did find gonioscopically peripheral synechiae confined to the posterior one-fourth of the trabeculae.

In cases of delayed reformation of more than six days, gonioscopic examination revealed very extensive peripheral synechiae which are clearly seen in the figures presented. This accurate plotting of the extent of the synechiae is a valuable record, which reveals from time to time the progression in the blocking of the angle, if any.

The fact that in all of these cases of secondary glaucoma, without exception, the authors found extensive peripheral synechiae, leads to this question: "Were the synechiae the cause of glaucoma?" The authors answer in the affirmative, although they are careful to state, "This view does not preclude the possible action of other pressure disturbing factors." In my opinion we should establish clearly the difference between primary and secondary glaucoma. In secondary glaucoma the hypertension is directly the result of the impeded outflow of ocular liquids. It may be only a transient symptom and disappear with the cause that blocked the angle and disturbed the outflow through it and the iris, or the obstruction may become permanent and bring about all the symptoms of true glaucoma. If we are able to recognize in time, by gonioscopy, the mechanical obstruction to the outflow, we may, by adequate measure, such as injection of air, irrigation of the anterior chamber, and resection of prolapsed processes, re-establish the patency of the meshwork and arrest the increase of tension.

On the other hand, there are cases in which primary glaucoma has been present before the extraction of the cataract or have shown symptoms later, in which one may find, as Doctors Kronfeld and Grossmann did in four cases, an entirely open or slightly closed angle.

In these cases the pathogenesis of increased intra-ocular tension and all symptoms associated with it is different from those of simple hypertension. Unfortunately, we do not yet know the cause or causes of primary glaucoma, but we do know that in it the obstruction of the outlets of the chamber by peripheral synechiae are the result and not the cause of increased tension.

MANUEL URIBE TRONCOSO, M.D., New York, N. Y.: I wish to congratulate Doctor McLean on his paper. I am very glad that the younger investigators give gonioscopy their attention and that they find this method important not only from the standpoint of research but also from the standpoint of clinical and surgical application.

The statistics of Doctor McLean with regard to the condition of the angle of the anterior chamber in the three kinds of glaucoma correspond entirely with my own figures, collected in three series of cases. Thus, in the chronic congestive type he found the angle open in 19 per cent of his cases, partially closed in 28 per cent, and entirely closed in 52 per cent. My own figures for this type of glaucoma were, respectively, 25 per

cent, 25 per cent, and 50 per cent. In non-congestive glaucoma he found a larger proportion of completely open angles than I did, amounting to 74 per cent. The angle was partially closed in 22 per cent and entirely closed in 3 per cent of his cases, while my own figures were 50 per cent, 38 per cent, and 5 per cent, respectively.

Doctor McLean has also confirmed my findings both in regard to the alleged sclerosis of the trabeculum and the deposit of pigment in this structure as a cause of non-congestive glaucoma, as reported by Dr. Otto Barkan. Gonioscopically it would be impossible to detect the sclerosis of the trabeculum, this condition being difficult to observe even with the microscope. The deposit of pigment in the meshwork is a senile condition, which may be seen in many eyes without glaucoma, while on the contrary there are many simple glaucomas in which no black pigment dots are observed.

The part of Doctor McLean's paper dealing with secondary glaucoma after cataract extraction shows the importance of gonioscopic examinations before and after operations. Following complicated extractions, uveitis sets in, and exudates can be seen in the angle blocking the meshwork. Even after uncomplicated extracapsular extractions, debris of the lens may accumulate in the chamber angle and produce hypertension. Hence, it is important to irrigate the anterior chamber after this kind of operation in order to remove all lens matter.

Doctor McLean, following Czermack, believes that the delayed reformation of the anterior chamber after extracapsular, and more rarely, intracapsular operations is the principal cause of secondary glaucoma. To avoid the peripheral synechia which causes this complication, he advises air injections into the anterior chamber.

I agree with Doctor McLean, when he asserts that there are two factors which predispose to closure of the opening after cyclodialysis, namely, extremely narrow angle and the clogging of the opening by blood coming from the surface of the sclera or spreading between the ciliary body and sclera.

I would like to call attention to the frequency of detachment and rupture of Descemet's membrane after cyclodialysis, which, in gonioscopic examinations, is seen hanging like a transparent, torn film over the angle. After successful cyclodialysis with magnesium implantation, the cleft appears patent, but we also should have in mind that there is a partial atrophy of the ciliary body with many alveoles due to gas cavities. This rarefaction of the tissues probably increases the aqueous overflow.

The findings of Doctor McLean in regard to complications after trephining operations are similar to those of Dr. A. Reese and myself. Gonioscopic examinations should be made before the operation to find the place where peripheral synechiae are not present and where the anterior chamber is wider. The prolapse and incarceration of the ciliary processes into the scar, which usually is unknown when a gonioscopic examination is not made after the operation, is a source of irritation and may lead to secondary infection and even to loss of the eye.

With the facilities for gonioscopy which the new gonioscope and new contact glass (that I presented yesterday before the Academy) gives to the practitioner, I hope this method of examination may become popular not only in glaucoma surgery, but also in cataract operations, and for the diagnosis of many other diseases present in the angle of the anterior chamber.

SANFORD GIFFORD, M.D., Chicago: I wish to discuss, very briefly, only the subject of glaucoma secondary to cataract extraction. I discussed a small series of such cases at the meeting in St. Louis for the benefit of the four or five people in the front row who were able to hear me, and I would like to emphasize again what Doctor McLean has so well brought out, the peculiar fitness of the cyclodialysis operation for glaucoma secondary to cataract extraction.

In five cases in which cyclodialysis was performed, gonioscopy was carried out afterwards by Doctor Puntenney, and in the successful cases it was found that the chamber angle was open, as Doctor McLean has shown so well.

The incidence of causes of secondary glaucoma in my series was quite different from that of Doctor Kronfeld's. In the first place, there were not many cases of delayed formation of the anterior chamber. Most of them were extracapsular cases, where cortex was left, where there was a moderate amount of iridocyclitis afterwards, and where there were small peripheral iris adhesions which actually could be seen with a loop, with the pillars of the iris adherent to the deep wound. It will be seen easily that cyclodialysis could be made to fit that situation very well. When an iridectomy has been performed, cyclodialysis is made in the area in which the pillar seems to be adherent, either the outer side or the inner side, or in the case of peripheral iridectomy it covers the whole area

of the iridectomy. Very often it is possible to see the iris brought right back into place when cyclodialysis is performed, just as you separate the pillar from the cornea.

I have carried out the idea of raising the patient in bed, and in addition I have used miotics. I think one has a better chance of keeping the new channel open if a miotic is used.

I have had only one case of secondary glaucoma in intracapsular operation. That was a case in which the anterior chamber was not formed for several days.

RODMAN IRVINE, M.D., Los Angeles: Doctor McLean has very aptly and concisely clarified the relationship of anterior peripheral synechiae to glaucoma. In this respect he confirms the observations of others, notably of Dr. Otto Barkan of San Francisco. In addition, Doctor McLean's findings indicate that so-called "trabecular glaucoma" is not a clinical entity determinable with the gonioscope. Further studies with varying techniques may not confirm this assumption.

Relative to trabecular glaucoma, I would like to know Doctor McLean's observations in exfoliation of the lens capsule. In the cases which have developed glaucoma, is it possible to see more capsular material in the angle than in cases of exfoliation without glaucoma?

A second point of interest to me was the reference to quiet iritis following trephine, and the inference that this condition results from incarceration of ciliary processes in the wound. Has Doctor McLean not seen incarceration of ciliary processes without resultant iritis, and quiet iritis without incarceration of the ciliary processes? We have felt that the low tension in these cases, resulting from over-effective filtration, may allow increase in the aqueous protein through altered capillary permeability. Posterior synechiae, which characterize the quiet iritis, form simply as a result of increased aqueous protein.

JOHN M. MCLEAN, M.D., Baltimore: There is very little to be said about what most of the discussers have offered because we seem to be in almost complete agreement. It is particularly gratifying to find that Doctor Kronfeld has been working on a problem of investigation exactly parallel to one on which I have been working, and that he has quite independently (neither one of us knew the other was working on it) come to exactly the same conclusion, with the exception of one very small matter. In that respect, I agree entirely with Doctor Castroviejo. His experiences with the corneoscleral suture in his cataract extractions and mine have been identical. Doctor Kronfeld implied in his remarks that corneoscleral sutures do not particularly help in preventing delayed reformation of the anterior chamber and subsequent glaucoma. I would merely like to mention again one word which I used in my text. I said "adequate" corneoscleral sutures, and I still feel that the study of a sufficient number of cases will show that an adequate corneoscleral suture will almost entirely prevent delayed formation of the chamber and almost entirely will do away with the secondary aphakic glaucoma from that cause.

Doctor Troncoso brought out one point on cyclodialysis which I omitted, and that is the detachment of the Descemet's membrane. I think we see it nearly universally, but as far as I have been able to determine, it has no effect on the outcome one way or another.

Doctor Gifford suggested the use of miotics after cyclodialysis. I did not mention that. I took it for granted that it was done almost always.

Doctor Irvine asked a few questions. First, about the exfoliation of the anterior lens capsule and its relationship to glaucoma. I did not attempt to cover that phase at all, because I think it is an entirely separate problem from that which I was attemping to discuss today. I believe that I could not answer it very adequately anyway, because I have not studied a large enough series to draw a definite conclusion one way or another. I do not believe one can take a small group of cases and decide this, that, or the other is a fact.

Doctor Irvine inquired about incarcerated ciliary processes. Yes, I have seen incarcerations with and without the so-called "quiet iridocyclitis." I did not mean to suggest that an incarceration necessarily implies a drawn-out iritis, but I think that it can be the cause.

Doctor Irvine also asked if we have seen iritis after trephining in the absence of ciliary incarceration. Yes, of course, but we have seen iritis in the absence of ciliary incarcerations not only after trephining but in a few instances after practically every trauma to the iris, whether it be surgical or otherwise.

PETER C. KRONFELD, M.D., Chicago: Doctor Castroviejo has said that in a series of 150 cataract extractions there were only two cases in which there was a 48-hour delay in restoration of the anterior chamber, and in no other case was there any marked delay.

Most of you probably have been wondering why we at the Illinois Eye and Ear Infirmary have such a high percentage of delayed restoration. I am inclined to think that the most important factor that brings about this delayed restoration is the lack of understanding on the part of the patient regarding what we are trying to do, and that lack of understanding is chiefly due to language difficulty. In so many instances it is not possible for us to convey to the patient the importance of absolute rest after the operation.

I did not mean to imply that corneoscleral sutures were of no particular value. It has been brought home to me very forcefully at the Illinois Eye and Ear Infirmary that the corneoscleral suture is a necessity. I only wanted to bring out the fact that delayed restoration is possible despite the presence of a good corneoscleral suture, and I think that is quite conceivable. The suture may bring about perfect apposition of the wound lips right in the center of the incision, whereas in one corner incarceration of lens capsule or iris might occur, entailing leakage of intraocular fluid.

I thoroughly agree with Doctor Castroviejo with regard to the advantages of a conjunctival flap which completely covers the incision. In all of my own cases of cataract I certainly see to it that the entire incision is covered by a conjunctival flap.

My associate and I greatly appreciate the kind words from the pioneer in the field of gonioscopy. I certainly did not mean to imply that I did not know or that I did not want to mention the fact that Doctor Troncoso had seen and reported peripheral anterior synechiae after delayed restoration of the anterior chamber. For the sake of brevity, I referred only to Czermak, the first author who had written extensively on this subject.

THE SIGNIFICANCE OF THE pH OF NASAL SECRETIONS IN SITU

NOAH D. FABRICANT, M.D.
CHICAGO

DESPITE the fact that scientific investigation of the pH mechanism began more than a half century ago, it is only very recently that the interest of practical technologists at large, and rhinologists in particular, has been aroused. Prior to this time, the subject of hydrogen ion concentration was poorly defined and lacked a clear, comprehensible terminology. With the advent, however, of comparatively new and simple methods for measuring hydrogen ion concentration, it has been possible to awaken the clinician's interest in a sphere of investigation that has practical application to innumerable and diversified fields. In the realm of medicine, the *pH influence* is intimately associated with general health. More specifically, in the case of blood, it is of paramount importance. This *pH influence* is not restricted to blood alone, for the pH of spinal fluid, lymph, and in fact all body excretions including the nasal secretions has very definite clinical significance.

It will be recalled that the pH scale, a means of expressing hydrogen ion values numerically, is today in common usage. The working range of the pH scale lies between 0 and 14. The midpoint of the range is 7 — the pH of pure water — which is the true neutral point. Values below pH 7 indicate an increased hydrogen ion concentration, or a predominance of the acid reaction, while values above 7 indicate an alkaline reaction.

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6-10, 1940, Cleveland, Ohio.

From the Department of Laryngology, Rhinology, and Otology and the Department of Pathology, University of Illinois, College of Medicine.

Heretofore, pH has been determined in one of three ways: by the hydrogen electrode, by the quinhydrone electrode, or by colorimetric procedures. These methods are highly involved and are subject to considerable error. Further, a factor not without importance is the consideration that biological fluids generally are very susceptible to changes in pH on almost instant exposure to air. This is particularly true of nasal secretions. To offset such a phenomenon, the usage of the glass electrode with its associated measuring equipment has made it possible to measure the pH of nasal secretions in situ with ease and precision.

Early in the course of my own investigations I was impressed by the fact that studies of the pH of nasal secretions accomplished elsewhere involved the collection of samples of nasal secretion either by suction or by having the patient blow his nose. Then, too, a frequent procedure was to record but one pH reading made daily on a sample of nasal secretion. While informative, a course of study of this type has distinct limitations, since the nasal secretions are not in situ, are susceptible to changes in pH on exposure to air, and are divorced from the normal milieu of the nose.

Some of the problems encountered are illustrated by Hilding[3] who employed a series of standardized indicators to test the pH values of a number of samples of nasal secretion collected during an attack of common head cold. The resulting pH indicated a definitely alkaline reaction, varying between 7.2 and 8.3. In order to determine the extent and speed of the changes in pH, single samples were tested from a patient with a

cold during the first 15 to 30 minutes. There was a change from 7.0 to 8.5 during a few minutes. Thereafter there seemed to be little or no change. Hilding found that the rapid change in pH during the first fifteen minutes was due to the loss of carbon dioxide gas that had been absorbed from the expired air as it passed through the nose.

In order to eliminate some of the disadvantages inherent in the methods employed elsewhere and to analyze further the wide range of pH findings reported, I decided to study the pH of nasal secretion in situ by utilizing a specially designed glass electrode in conjunction with the Coleman electrometer. By conducting minute-to-minute readings of the pH values of nasal secretions in situ and graphically charting the results in a group of patients observed daily for more than an entire year, it is possible to explain satisfactorily the wide range of pH determinations revealed elsewhere by workers employing other methods of procedure in cases where the nose was clinically normal, and in cases of acute rhinitis, acute rhinosinusitis and allergic rhinitis.

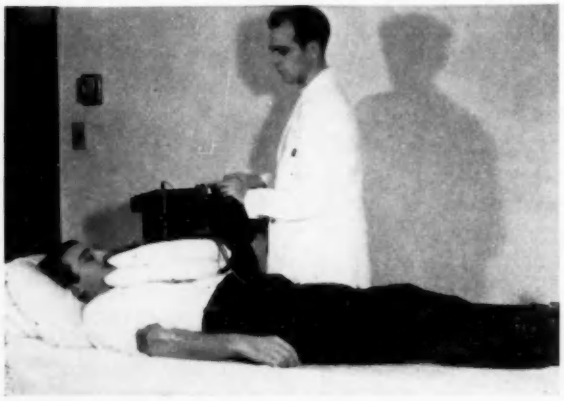


FIG. 1 — The position of the patient in determining the pH of nasal secretions in situ.

Method. —The Coleman electrometer is used in the determination of nasal pH. The calomel half-cell is utilized as a reference electrode making contact with the patient by means of a salt bridge. The salt bridge contains a saturated solution of potassium chloride which is separated from a physiological saline solution by a plug of agar prepared in a concentrated solution of potassium chloride. The reference cell is submerged in the potassium chloride solution. The machine is standardized by submerging both the salt bridge and the glass electrode in a small beaker filled with Sorensen's buffer solution.

The nasal glass electrode is inserted into the patient's naris and is left resting on the floor of the nasal passageway in contact with the inferior turbinate. The tube containing the salt bridge makes contact with the patient by being placed on the cheek of the opposite side of the face, immediately lateral to the opposing naris. The salt bridge is placed on the side opposite to the glass electrode.

It is advisable that both the glass electrode and the salt bridge rest upon a specially constructed pillow lying on the patient's chest. This will eliminate any shifting of the electrode and the salt bridge, for unnecessary movement will

distort the accuracy of the readings. The patient should remain as quietly as possible. Readings are taken each minute (Fig. 1).

The pH of nasal secretions in situ describes a cyclic and rhythmical series of high and low points (Fig. 2).

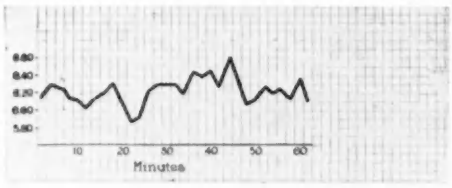


FIG. 2 — A graphic charting of the pH of nasal secretions in situ. Minute-to-minute recordings have been taken for a period of one hour.

At no time does the pH remain constant over an appreciable length of time. I find that the so-called normal fluctuations of nasal pH, from approximately 5.5 to 6.5, in a clinically normal nose appear to follow a definitely correlated rhythm. The futility of relying upon only one pH reading is amply illustrated by the frequent numerical changes in pH values that occur when readings are recorded over a period of one hour or more. Particularly do I wish to emphasize this phenomenon, since it would be a mistake to standardize or to press all observations into definite and fixed levels and apply these levels to the individual, quite overlooking the fact that each individual chemical level can be considered only in relation to that individual at some particular time and under certain conditions and none other. In so doing we may miss the exquisite rhythm that is so obvious when minor changes are followed in the nasal pH from day to day, from hour to hour, yes, from minute to minute!

Petersen[7] has demonstrated that in our concern with the pH level we have before us one of the major balances with which every organic and inorganic reaction is integrated. For the time being, I merely shall call attention to the fact that the nasal pH varies with sleep, with rest, with the ingestion of food, diurnally and nocturnally, and that it can be changed not only by infection but by alterations in an indvidual's emotions. The significance of fluctuations in pH must be understood, because with such changes, permeability of membrane and stimulation of tissue — indeed every phenomenon of pathologically altered tissue — will naturally be reflected in the changing milieu of the cells. The nasal pH can be said to mirror a whole series of functional as well as chemical changes which may be of clinical significance in the inadequate organ, or for the organism as a whole. An understanding of the peaks and intervening troughs perhaps may contribute to an understanding of the beginning of nasal disease processess.

The rhythmical series of undulating high points and low points, which nasal pH describes, is a biological phenomenon that is equally true of other surfaces of mucous membrane about the head and neck, as well as of those of the skin. pH studies were made of the buccal mucosa, the lips, various portions of the tongue (Fig. 3), and of the gingiva at intervals of one and two minutes. The same cyclic rhythm, which is true for nasal pH, is also true for the buccal mucosa, the

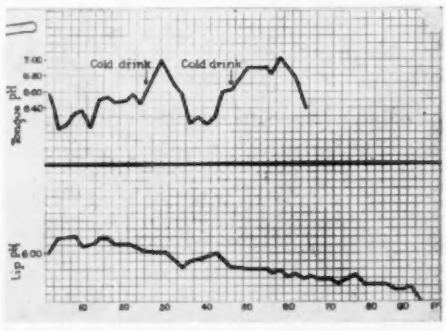


FIG. 3 — pH of the secretions on the tongue and the lip. A drift toward alkalinity followed a cold drink of water.

lips, the tongue, the gingiva and the skin. At this point, I may venture to add that a similar rhythm can be found for the pH of vaginal mucosa and rectal mucosa, and in fact any surface of the body that readily lends itself to glass electrode study in situ. It is quite conceivable that this method of study, when applied to these regions, may bear definite therapeutic fruit.

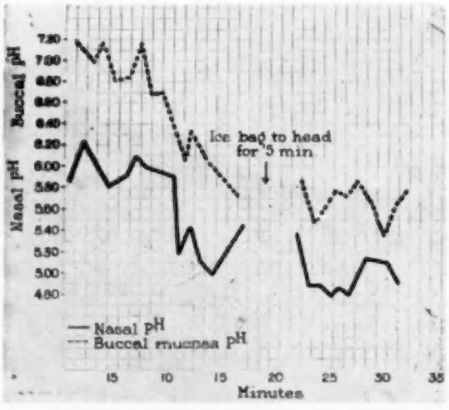


FIG. 4 — The effect of an ice bag applied to a patient's head on the course of the pH of the secretions of the nose and buccal mucosa.

and was distributed in its parallelism only by the application of an ice bag to the patient's head (Fig. 4).

Similarly, in measuring the pH of the tip of the tongue and of the buccal mucosa, the pH rhythm of the two surfaces again ran parallel to one another. However, shortly after the patient drank a half glassful of water, the parallel rhythm of the associated pH values was broken (Fig. 5). Since when drinking cold water a greater area of contact is produced on the tongue by the water than on the buccal mucosa, the effect is

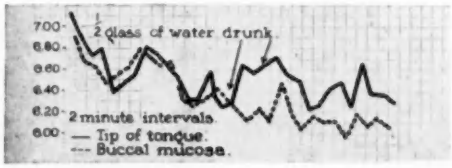


FIG. 5 — The effect of cold water on the pH of the tip of the tongue and the buccal mucosa.

that of a more pronounced trend toward alkalinity in the tongue than in the buccal mucosa. The undulating pH rhythm of the skin, too, is affected by friction

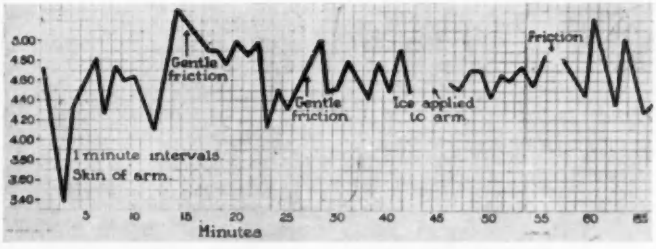


FIG. 6 — The effect of friction and ice on the pH of the skin.

In one of my earliest experiments I attempted to correlate a relationship between the pH of nasal secretions and that of buccal mucosa by charting the pH values obtained during alternate minute-to-minute readings. In a general way, it was found that the fundamental rhythm of both of these mucosal surfaces progressed in a parallel manner and by the application of ice to the skin (Fig. 6).

The course of nasal pH rhythm is altered by the application of either cold or heat. An ice bag applied to each side of the nose for a period of twenty minutes produced a drift upwards, that is, toward alkalinity. When the ice bag was removed, the shift in nasal pH descended

toward a more acid status. The effect of heat was readily demonstrated by a characteristic response — one that is diametrically opposed to that of cold. An electric heater-lamp, placed at a distance of two feet from the patient's face, was permitted to glow for twenty minutes. At the end of this time, the nasal pH proceeded to drop — it became more acid (Fig. 7). Again, spraying cold water into the nasal passageway produced a drift toward alkalinity, while the spraying of warm water provoked a drift toward acidity. These characteristic responses of the course of nasal pH to cold and heat could be repeated again and again.

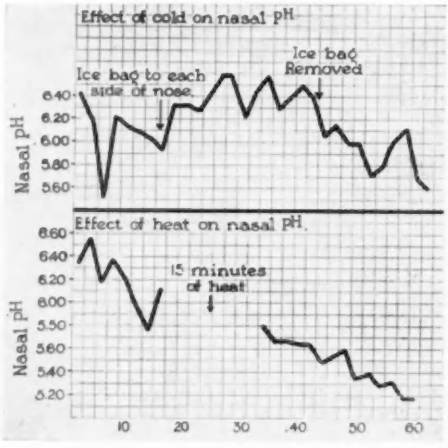


FIG. 7 — The effect of cold and heat on nasal pH.

A series of experiments then was conducted to study the effect of a group of nasal vasoconstrictors manufactured by various pharmaceutical laboratories throughout our country. Before beginning these experiments I was convinced that all of the vasoconstrictors would alter the rhythm of the nasal pH in a like manner. To my great surprise, they did not. The following list includes the nasal vasoconstrictors utilized, together with the pH as given by the medical directors of the various pharmaceutical laboratories and corroborated by me:

Metaphedrin aqueous	9.5
Metaphedrin isotonic	9.5
Benzedrine solution (when applied to nose)	8.0
Isohalant	6.
Glucofedrin	5.4 to 5.8
Adrenalin inhalant 1:1000	2.3 to 2.5
Synthetic epinephrine 1:1000	3.7
Ephedrine hydrochloride 1% in saline	5.9
Propadrine hydrochloride 1%	4.8 to 5.0
Neosynephrin hydrochloride ¼%	3.53 to 4.23
Neosynephrin hydrochloride 1%	4.1 to 4.23

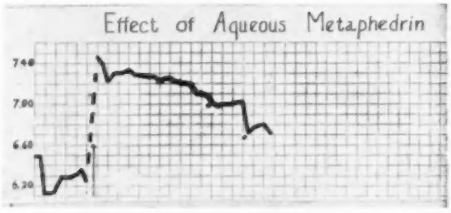


FIG. 8-a

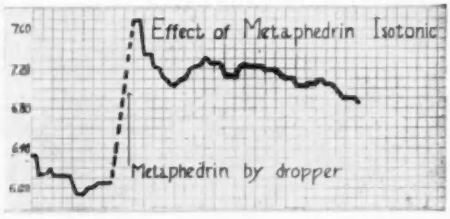


FIG. 8-b

FIG. 8 — The drift in nasal pH rhythm toward alkalinity induced by metaphedrin aqueous and metaphedrin isotonic solutions.

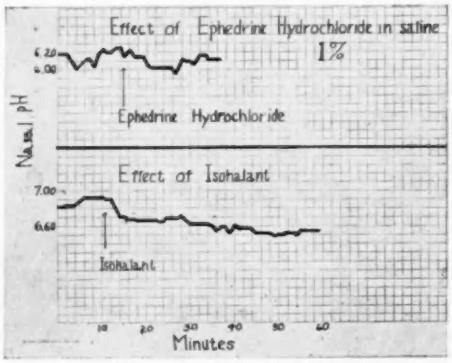


FIG. 9 — The relatively even tenor in nasal pH produced after the use of 1% ephedrine hydrochloride in saline and by isohalant. Similar responses follow the administration into the nose of 3% ephedrine hydrochloride and glucofedrin.

It will be observed that the pH of the nasal vasoconstrictors vary markedly from an acid 2.3 to an alkaline 9.5. It soon became evident to me that the manner in which the trend of the nasal pH rhythm is affected depends entirely upon the pH of the drug employed. Thus, drugs like metaphedrin aqueous, metaphedrin isotonic (Fig. 8), and benzedrine solution, acting with a highly alkaline hydrogen ion concentration, induce a marked drift in the nasal pH rhythm toward alkalinity. Drugs with a pH range of 5.5 to 6.5, such as 1% solution of ephedrine hydrochloride in normal saline, glucofedrin, and isohalant — drugs approximating the normal fluctuations of nasal pH — do not markedly affect the nasal pH one way or another when the nasal pH study is carried out for a period of one hour and when the nasal pH for that particular day swings within the normal range (Fig. 9). Drugs with a pH level of less than 5 induce a noticeable drift downward in the nasal pH, that is, toward acidity. Within this group lie both neosynephrin preparations, synthetic epinephrine 1:1000, adrenalin inhalant 1:1000, and to a lesser extent, propadrine hydrochloride 1% (Fig. 10).

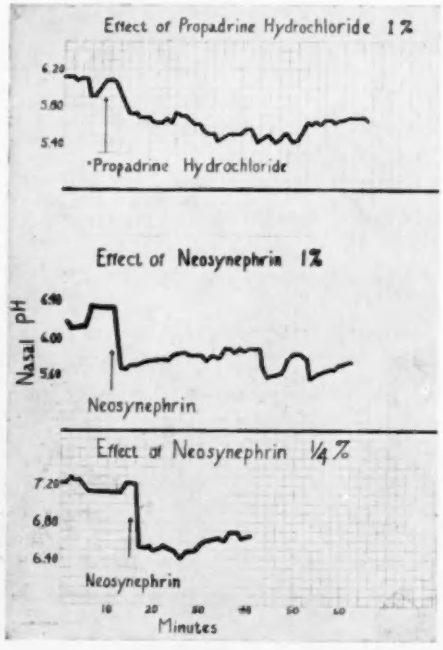


FIG. 10-a

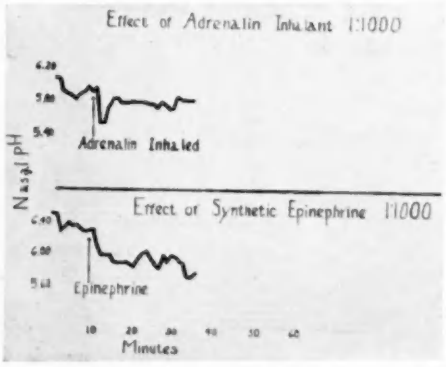


FIG. 10-b

FIG. 10 — The drift toward acidity in nasal pH produced by neosynephrin hydrochloride: 1% and ¼%, propadrine hydrochloride: 1%, adrenalin inhalant: 1:1000, and synthetic epinephrine: 1:1000.

On many occasions the drift in the nasal pH was prolonged for an hour, and frequently longer, thus permitting sufficient time to elapse for alterations in permeability of nasal capillaries and permeability of nasal membrane. On other occasions the nasal vasoconstrictors altered the drift in nasal pH for shorter periods of time. This phenomenon affords many interesting problems, for unquestionably in such instances not only must the ever-changing role of the host be considered but also the effect of temperature and barometric pressure on the action of drugs. That drugs act differently under changes in barometric pressure and temperature has been shown by Macht[4] in his experiments with digitalis and by Nedzel[6] in his work with morphine.

The use of the benzedrine inhaler produced a marked rise directed toward an alkaline status when two inhalations were made by the patients. The change in nasal pH became dramatically evident

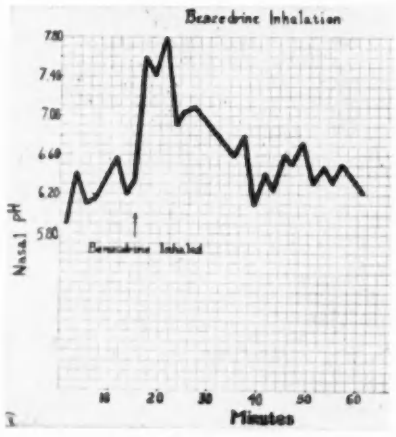


FIG. 11 — The alkaline response in nasal pH to the benzedrine inhaler.

within one or two minutes (Fig. 11). When the benzedrine was inhaled through one naris, the nasal pH was affected only in that particular naris, whereas the unaffected nasal passageway showed no change in nasal pH. But as

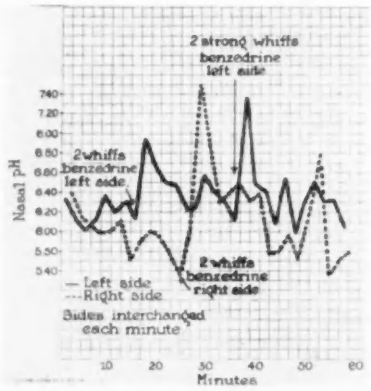


FIG. 12 — The effect of benzedrine inhalation on nasal pH when applied to alternate nasal passageways.

soon as the unaffected naris was subjected to an inhalation from the benzedrine inhaler, a marked drift toward an alkaline status in nasal pH was soon discovered (Fig. 12).

To establish further the effect of alkaline and acid solutions on the course of nasal pH rhythm, two solutions were used — Sorensen's solution with a pH of 8.36 and dilute acetic acid with a pH of 3.35. When sprayed in the nose, the dilute acetic acid attracted the nasal pH toward a definitely acid status, while Sorensen's alkaline solution drew the course of the nasal pH toward a markedly characteristic alkaline status.

Hilding,[2] collecting samples of nasal secretions, observed that the pH rose slightly and became more alkaline during the first four days of an attack of acute rhinitis. Mittermaier[5] found that in cases of acute inflammation, the pH of the nasal secretions he collected was definitely on the acid side. My own studies of the pH of nasal secretions in situ during an attack of acute rhinitis parallel the findings of Hilding. For the most part, I find that the pH of nasal secretions in situ during attacks of acute rhinitis and acute rhinosinusitis is alkaline—the secretions are more alkaline than normal. This finding has clinical significance, for those nasal vasoconstrictors which can lower the nasal pH from an abnormal alkaline status to a desirably normal acid status may perform a valuable function. Conversely, those vasoconstrictors which either raise, enhance, or perpetuate an alkaline nasal pH during the stage of acute rhinitides may prolong an undesirable status of nasal pH, a status in which the bacteria accompanying the acute infection find a fertile field for growth. It is more than likely that during an alkalosis of the nasal mucosa, changes in capillary, arterial and membraneous permeability proceed at so significant a pace as to prolong an abnormally physiological nasal environment.

At this time, I would like to interject that work is being done to show that the number of bacteria which can be recovered from the nasal mucosa at high and low points in the nasal pH rhythm differ astonishingly in number. This evidence will be presented at some future occasion.

To proceed, vasoconstrictors possessing an unusually high pH value merely may serve to disrupt the normal pH value of nasal secretions found in the clinically normal nose, enhance irritation of the nasal mucosa, and postpone the return to a desirably normal pH status. It is therefore suggested that during attacks of acute rhinitis and acute rhino-sinusitis the employment of a nasal vasoconstrictor, which lowers the alkaline pH to a level between 5.5 and 6.5 (approximating the normal pH status of nasal secretions in situ), is most desirable. This, of course, implies that there be a standardization of the pH values of the various nasal vasoconstrictors now available to the American public. Contrary to the generally accepted American advertising slogan, it is now time to acidify the nasal mucosa — not alkalinize!

A study of the pH of nasal secretions in cases of nasal allergy suggests a similar state of affairs. Buhrmester[1] found that nasal secretions collected from cases of nasal allergy were for the most part predominantly alkaline, but instances were noted in which the pH remained acid. These findings were supported substantially by my own studies of nasal secretion in situ. An alkaline status of the nasal secretions was seen during the active stages of allergic rhinitis. The nasal pH descended to the neutral point and to the acid status when clinical improvement was felt by the patient. Whenever the symptoms became aggravated, a return to alkalosis was detected. Therapeutically, the implications for the desirable pH of nasal vasoconstrictors becomes obvious. As in the case of the acute rhinitides, I believe that the usage of an appropriate nasal vasoconstrictor implies one that will lower the alkaline pH to a normal acid level between 5.5 and 6.5.

Finally, a brief investigation was made of the effect of vasodilators on the nasal pH rhythm. Since I was unable to obtain a satisfactory nasal vasodilator, I employed two drugs that are frequently inhaled during attacks of angina pectoris. These were amyl nitrite pearls and trichlorethylene — a Calco preparation. The usage of these drugs suggested a slow drift in the nasal pH rhythm toward acidity (Fig. 13).

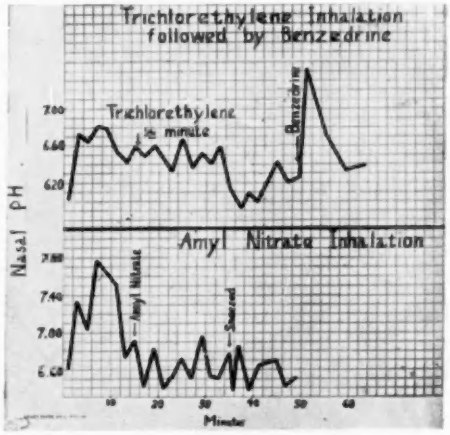


FIG. 13 — The slow drift in nasal pH suggested by the inhalation of amyl nitrite and trichlorethylene. The characteristic rise to alkalosis occurs after an inhalation of benzedrine.

SUMMARY AND CONCLUSIONS

With the advent of comparatively new and simple methods for measuring hydrogen ion concentration, it is possible to awaken the clinician's interest in a sphere of investigation that has practical application to innumerable and diversified fields. To offset the fact that nasal secretions, when collected, are very susceptible to changes in pH on almost instant exposure to air and are divorced from the normal milieu of the nose, the use of the glass electrode with its associated measuring equipment, the Coleman electrometer, has made it feasible to measure the pH of nasal secretions in situ with ease and precision.

By conducting minute-to-minute readings of the pH values of nasal secretions in situ and graphically charting the re-

sults in a group of patients observed daily for more than an entire year, it has been possible to explain adequately in cases where the nose is clinically normal, and in cases of acute rhinitis, acute rhino-sinusitis, and allergic rhinitis the wide range of pH determinations revealed elsewhere by workers employing other methods of procedure.

The pH of nasal secretions in situ describes a cyclic and rhythmical series of high and low points. At no time does the pH remain constant over an appreciable length of time. The normal fluctuations of nasal pH in a clinically normal nose — from approximately 5.5 to 6.5 — appear to follow a definitely correlated rhythm. The futility of relying upon only one pH reading is amply illustrated by the frequent numerical changes in pH values that occur when readings are recorded over a period of one hour or more.

The course of nasal pH rhythm is altered by the application of either cold or heat. Cold produces a drift towards alkalinity, heat a drift towards acidity. The pH of nasal secretions in situ is alkaline during an attack of acute rhinitis, acute rhino-sinusitis, and the more active phases of an allergic rhinitis. This finding has clinical significance, for those nasal vasoconstrictors which can lower the nasal pH from an abnormal alkaline status to a desirably normal acid status — a pH level between approximately 5.5 and 6.5 — may perform a valuable function. Conversely, those nasal vasoconstrictors which either raise, enhance, or perpetuate an alkaline nasal pH during these rhinological conditions may prolong an undesirable status of nasal pH.

It is suggested that during attacks of acute rhinitis, acute rhino-sinusitis, and the more active stages of allergic rhinitis, the employment of a nasal vasoconstrictor which lowers the alkaline pH to an acid level between 5.5 and 6.5 is most desirable. It is suggested further that there be a standardization of the pH values of the various nasal vasoconstrictors available at the present time to the American public. Contrary to the generally accepted American advertising slogan, it is now time to acidify the nasal mucosa — not alkalinize!

REFERENCES

1. Buhrmester, C. C.: Study of hydrogen ion concentration, nitrogen content and viscosity of nasal secretions, Ann. Otol., Rhin. & Laryng. 42:1041-1057 (Dec.) 1933.
2. Hilding, A.: Common cold, Arch. Otolaryng. 12:133-150 (Aug.) 1930.
3. Hilding, A.: Note on some changes in hydrogen ion concentration of nasal mucus, Ann. Otol., Rhin. & Laryng. 43: 47-49 (March) 1934.
4. Macht, D. J.: J.A.M.A. 98:103, 1932.
5. Mittermaier, R.: Unterscuchungen über die Wasserslofflonenkonzentration an Sekreten und Schleimhäuten, im besonderen bei chronischen Nebenhablenerkrankungen, Arch. f. Ohren,-Nasen-u. Kehlkopfh 127:1 (Dec.) 1930.
6. Nedzel, A. J.: Pressor episodes, diets, and toxicity of morphine sulfate, J. Lab. & Clin. Med. 23:1063-1068 (July) 1938.
7. Peterson, Wm. F.: The Patient and the Weather, Ann Arbor, Mich., Edwards Brothers, 1936, vol. 1 part II.

DISCUSSION

ANDERSON C. HILDING, M.D., Duluth: Doctor Fabricant's paper came to my desk in the mail at the beginning of a busy forenoon at the office. I opened the envelope and glanced at the opening paragraph, then became so fascinated that I read every word while the patients waited. It seems to me that Doctor Fabricant has shown us another major step in the progress toward an adequate knowledge of the physiology of the nose, and we owe him a debt of gratitude.

My own interest was especially aroused inasmuch as Doctor Osterberg, of the Mayo Clinic, and I had planned just such a study some years ago. We got as far as the electrode, and then I left Rochester and had to carry on the study alone with the old methods, the results of which Doctor Fabricant has cited so well.

There are many gaps in our information that now perhaps can be supplied. What happens to the pH of the nasal secretion when one's feet get wet and cold? When one sneezes after being exposed to a draft, has

the pH changed? When a cold develops, does the drift toward the alkaline side begin early enough so that it possibly could be the cause of symptoms or is it only an effect of the symptoms? Is the change on the surface of the mucous coating only or does it go deep into the cells? Is there a seasonal change in the pH? What happens to the pH in the presence of rhinitis associated with various diseases such as poliomyelitis, measles, and influenza? What is the effect of fever? What about bacterial growth? Is there a variability in pH depending upon the type of organism present? What about the action of lysozyme which is so sensitive to pH concentration? Does it have any effect upon the recently described virus-inactivating enzyme which is normally found in nasal secretions? Doubtless the author cannot answer these and many other questions as yet, but the possibilities are great. It is to be hoped that he will pursue his studies until many of these questions become clarified.

I should like to ask some questions which no doubt can be answered at this time.

The curves which he has shown indicate rather wide and rapid changes in the pH. There is marked variability—hardly a rhythm as we think of rhythms in respiration, heart cycle, pulse curves, blood pressure, and so on. Has he made control observations on solutions of a known constant pH, on gels, or a piece of meat over an extended period in order to make sure that the variability at least in part is not in the method? One would think that there must of necessity be considerable variation in the contact between the electrode and the mucous coating. Could part of the variability be due to CO_2 variations? This could be determined for instance if readings were taken alternately just at the end of inspiration and just at the end of expiration. One would expect the variation during respiration to be as rhythmical as breathing itself.

Doctor Fabricant states that it is desirable to reduce the high alkalinity of the nasal secretion during acute rhinitis. He may have good reasons for reaching that conclusion, but if so, he does not give them in his paper. It may be desirable to reduce the alkalinity but the mere fact that the pH is high during rhinitis whereas normally it is low does not of itself indicate that it is desirable to reduce it during this condition. The leukocyte count may be 20,000 during pneumonia, but we do not attack the leukocytes and try to reduce the count just because the desirable normal is 8,000. We know that leukocytosis is one means by which nature attacks the disease. Might it not be that the drift toward alkalinity in the nasal secretion is a purposeful reaction even as fever in disease is a purposeful reaction? My own instinct would lead me to consider it as such until there were evidence to the contrary. We have known for some years now that there are certain other phenomena that occur during this drift of pH during rhinitis. As the reaction becomes more alkaline, the epithelium becomes looser, and by the time it reaches 9 the epithelium definitely begins to break up. Untold millions of living ciliated epithelial cells shake themselves loose and float away in the secretion. Is this due to the destructiveness of the cause of the common cold, or is it a purposeful reaction on the part of the epithelium? No open lesions result, and the epithelium does not seem to suffer, but what could possibly be the purpose of such floating cells in a thin secretion which drains away in a few moments anyway? To say, however, that it is purposeless is in my opinion an unwarranted assumption. Now there comes a hint in a recent number of Science News Letter (September 28, 1940), from Francis of New York University Medical College, that epithelial cells in the respiratory tract are sloughed off and replaced under certain conditions with a different type of more resistant cell. Before we set out now to acidify the sniffling American, let us be very, very certain that we are not breaking a link in a purposeful chain of events by virtue of which nature will cure the sniffles if let alone.

Doctor Fabricant states that patients with hay fever feel worse when their secretions are alkaline and better when they are acid. Are the symptoms which the patient feels due to the alkalinity or is alkalinity only one of the accompanying signs? Do the patients on whom he uses Sorensen's solution develop the discomforts of the hay fever sufferer?

Let me thank Doctor Fabricant again for this splendid contribution. The fact that I do not go quite so far in conclusions as he in no way detracts from the value of his work.

WILLIAM F. PETERSEN, M.D., Chicago (by invitation): Doctor Fabricant has brought out three important points in these observations on the nasal pH.

In the first place, he makes the observation that a random determination of the nasal pH is of little significance. This is because of the change in the level that is constantly going on if one observes the membranes long enough. As a result of these constant changes the possible influence of drugs must be evaluated on the basis of long continued obser-

vations before, as well as after, the agent has been applied.

In the second place, Doctor Fabricant further observes that the abnormal mucous membrane exhibits a trend to fixation of the membranous state, namely, the pH level remains relatively fixed. Thus it differs wholly from the normal condition which allows continuous adaptation to environmental situations. Indeed, it is this autonomic fixation which is fundamentally responsible for the various evidences of clinical dysfunction. Only when the normal ability is restored is proper function returned to normal. It would seem probable that some of the pharmacological agents studied by Doctor Fabricant exert effects in this direction.

In the third place, it is evident that, apart from the active pharmacological principles involved (acting directly on the cells of the mucous membranes, on the nerve endings, or on the capillaries), the pH level of the agent itself (or of its vehicle) is of some significance in a possible therapeutic effect.

From the implications of the function of the nasal mucous membranes, as well as the evolutionary history, it might seem self evident that the organ must normally be able to adjust itself perfectly to changes in the gases passing the surface. Possibly it will be useful in mediating more far-reaching adjustments of the organism in general to changes in the gaseous atmosphere in which the organism exists. These adjustments may be mediated through the rich vascular or nervous network, possibly even more directly through old connections of the olfactory tract and those basal parts of the central nervous system which have so much to do with the autonomic integration.

After all, though organic life began in the sea, we, as mammals, have survived in a gaseous medium and apart from the skin. The nose is our next and possibly even more important region of contact and seat of what Hippocrates called "intelligence coming from the air."

In the case of our lower mammalian brethren the "intelligence coming from the air" through the nose is of vast significance for survival. Possibly we have developed beyond that state. However, if I may judge from the amount of trouble that physicians have with the upper part of the respiratory tract, some of these fluctuations in the nasal mucous membranes possibly may deserve more detailed study of the type that Doctor Fabricant has developed.

NOAH D. FABRICANT, M.D., Chicago: I wish to thank the gentlemen for their remarks.

Doctor Hilding has asked a number of pertinent questions. Not all of them am I able to answer because this is, as you can readily observe, a new field of development. I have really opened the door, and I do invite those investigators throughout the country who are interested in this field of work to come in, because the nasal secretions are fine!

Now, Doctor Hilding questions the desirability of a return to a relatively normal and slightly acid state. In a general way, I believe it is desirable, because all our efforts, as far as therapeutic medication in the nose is concerned, are so directed as to convert abnormal nasal conditions to a normal physiological status.

One may question the idea of using drugs at all. We do use them, however, and we are going to continue to use them, because for the time being all of us believe in the efficacy of some form of medication, even though it may be limited.

As far as the use of the term "rhythm" is concerned, I think rhythm can be either classed as irregular or regular. It may be undulating. We can speak of irregular regularity or regular irregularity. For lack of another word to describe the situation, we will say that it is a broken, undulating type of rhythm.

As far as controls are concerned, I believe that a valid suggestion has been made by Doctor Hilding. I shall pursue further experiments in that direction. In a general way, perhaps I can give a partial answer.

I checked the pH of the various nasovasoconstrictors used as shown on the slide, and I verified the pH to be the same as the various medical directors of the different pharmaceutical laboratories claimed. You will admit that it takes a little time to ship merchandise; before the consumer receives his bottle of nasovasoconstrictor a number of weeks have passed. In general, I found that the pH in the solution remained the same some weeks later, after it had been sent out by the laboratory.

In answer to a number of questions which Doctor Hilding has asked, my answers are as follows:

I have found that the nasal pH is lower at night than it is during the daytime (this is a preliminary observation, and I will have to check and recheck my findings).

The pH of nasal secretions rises after the ingestion of food.

Emotions have a definite effect in breaking up the regularity or irregularity of the undulating rhythm.

AN APPRAISAL OF VISUAL DEFECTS IN INDUSTRY

(Based on a Study of 16,332 Cases)

HEDWIG S. KUHN, M.D.
HAMMOND, INDIANA

IN THE tremendous and developing field of American industry there are challenges to Ophthalmology that are not being faced and opportunities for service that have not been seized. There has been considerable study of industrial eye hazards of every description, of lighting in industry, of educational eye conservation programs, and so on, but an extensive or detailed analysis, as far as we have been able to discover after diligent search, has not been devoted to an appraisal of visual defects as they exist in industry. There have been no scientific evaluations of methods of visual testing of employees in *industry*, such as have been made in the schools. Physicians have not directed their attention to the rapidly changing demands which modern machinery makes on visual performance as distinguished from visual acuity alone, nor have Industrial Ophthalmologists yet devoted their attention to an intimate sharing of the production and efficiency problems of management (now so tragically sharpened by war demands). Little thought has been given to the establishment of practical visual standards which vary according to the requirements of specific jobs. "Eyes for the Job" is the concept which has dramatically but realistically grown from the heart of this research project. It was an amazing and rather awesome experience to have swung open to me great gates of industries dealing in Chemicals, Big and Little Steel, Soap, Public Utilities, Textiles, Tanks, and even Horse Shoes.

The three great epochs in the development of American industry are shown in figure one. These comprise efficiency in perfecting tools, the machine itself, efficiency in handling raw materials, and finally the present day phase, human efficiency, or skill, which concerns us as medical consultants.

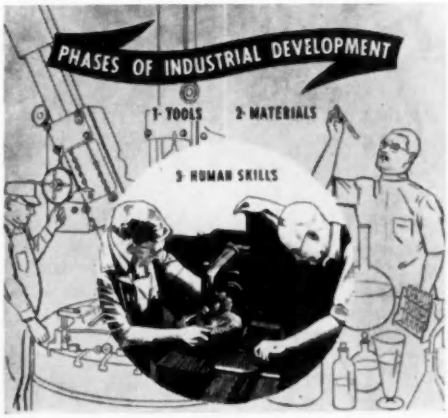


FIG. 1 — *Phases of Industrial Development* — Three phases in the development of modern industry. Adapted from comments in *Eye Hazards in Industrial Occupations* by Resnick and Carris.

Because the labor specifications for any modern industry are expressed in terms of sustained attention, correct perception and quick reaction, visual aptitudes as well as manual and intellectual aptitudes, have been brought sharply into the focus of industrial management. The great apprentice training programs, both governmental and privately subsidized, to provide an adequate number of skilled laborers, rest on the as-

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6-10, 1940, Cleveland, Ohio.

sumption of physical health and aptitudes, and especially on minimum requirements of visual performance. Ophthalmologists in industrial communities will be called on more and more to work with industry inside its plants and with its departments of employment and personnel as well as continuing to take care of injured eyes. Pointed challenges which are of immediate concern are thereby offered to us.

Industrial Ophthalmologists have not had much training in this field in medical schools, in postgraduate courses, or in literature to assist them. Practicing in the region aptly called "The Rhur Valley of America," we, as consultants to industry, early faced this blank wall — this void — and were forced to dig in and seek answers to the insistent needs that arose. Only the high spots of the enormous field which was available for scrutiny can be touched on in the allotted time. The vistas of an ever widening field of application, the many freshly revealed angles still unexplored, the services yet to be rendered are indicated, but not developed, in this paper.

Most of all, I would have liked to delve more fully into the industrial problems that are solved only by a *full* understanding of visual performance as it is related to specific jobs, a concept which aviation in particular has found necessary for a long time. But at this time I can but use as a basis the statistics accumulated which I have tried to make as graphic and alive as possible.

This survey, as reported to date, is based on the test findings of the visual performance of 16,332 employees, which means that over 100,000 separate test items have been recorded. It consists of recordings of visual acuity with and without the employee's correction, stereopsis ratings, color vision, and phoria readings for distance and near in the cases of employees whose age, sex, race, and occupation were also recorded. The telebinocular was used in each case to get this data. In addition, for correlation, and for making special studies, the Snellen chart was used, Green's refractor (for duction and near point study), rotary prism, Maddox rod and Maddox wing test (for special phoria measurements), and the Ishihara test for color comparison. In order to study the demands made on eyes under every type of industrial work, there was needed and secured a large range and variety of occupations, as figure two demonstrates. For comparison, I refer to a crane operator, dependent in a large measure on stereopsis at 150 *feet* for both safety and efficiency, and a looper doing piece work eight *inches* distant from her eyes, in whose case the contents of her pay envelope are dependent on her visual aptitudes.

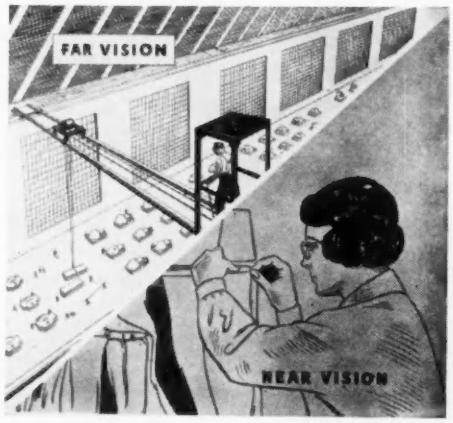


FIG. 2 — *Far Vision — Near Vision* — **Typical differences in the circumstances requiring critical vision in industry; difference in the distances of vision required of a crane operator and a looper in a hosiery mill.**

A staff of expert, experienced lay technicians conducted the individual tests under my personal supervision. They carried out a program which I originated in every detail. They followed

rigid rules of conduct and procedure, made exact and uniform individual records, made no interpretations themselves of these records, and made no comments to the employees being tested or to the management. This staff was made available by the generous cooperation of the Statistical and Scientific Departments of Bausch and Lomb Optical Company.

If I had kept pedometer readings of the endless miles that I have walked supervising the procedure of the testing units or of the hours spent in consultation with the management regarding methods and policy, safeguards against criticism of any kind, and insistence on scrupulous ethics before, during, and following the surveys, I am sure it would be established forever that medical guidance, supervision, and control, with the cooperation of the management, are absolutely essential in a field so liable to commercial exploitation. The actual testing, however, not only can be, but perhaps had better be, done by laymen.

In evaluating the present techniques generally used by Company Doctors for eye examinations of applicants, we found that, with few exceptions, they were totally inadequate. Our opinions are shared by the Medical Directors of those few large industries whose equipment is complete for binocular tests, as expressed by Dr. G. H. Gehrmann, Medical Director of the du Pont Corporation, "We have found the binocular technique, including additional tests to those of acuity, far superior to any other method used." The complicated procedure in eye testing such as that carried out for aviation by Colonel A. D. Tuttle, Medical Director of the United Air Lines, also corroborates our experience.

Visual acuity taken by the Snellen chart is unreliable because of (1) the usually unsatisfactory lighting of the chart; (2) the inaccurate distances used from the chart to the individual to be tested; (3) the deception used by employees in memorizing charts (which in areas like ours has become a real art); and (4) the fact that the Snellen chart permits only a monocular acuity test.

The color test where both yarn and Ishihara are used are too often inaccurate because the cords or yarns become soiled or the test is given too hastily. Also, what is of utmost importance, the tests are given arbitrarily so that color deficiencies are not graded according to the requirements of the job.

Phoria tests for distance or near are not used generally and are not recognized as important in the present set up. Stereopsis recordings are not being made routinely. Visual performance tests for close work are not being made.

Faced with the need of setting up a more complete technique for testing, consideration was given to the development of one that would give all necessary information, one that would be scientifically sound, and one that would require a minimum amount of time and would represent a maximum degree of practical accuracy.

We came to the conclusion that a binocular instrument was essential. It would have to be sturdy and portable and should incorporate the complete equipment for visual performance tests sufficiently foolproof to eliminate accidental factors. It was deemed essential that record forms be simple and practical, making data quickly available for medical reference, merit ratings, and production analysis. Also necessary are interpretation of tests which have been carefully worked out and graded on the basis of visual requirements and safety hazards for various types of occupations in various industries. This interpretation should be reviewed by a medical adviser who has a thorough knowledge concerning the job itself and the management's problems.

Complexity of record forms, highly impractical and theoretical interpretations, and needless intricacy of targets used, which are elements leading to confusion, have been the most serious faults of the telebinocular, particularly as it applies to industry. Studies of the accuracy of the instrument itself have shown it to be scientifically sound, but have shown it to be adapted primarily to the study of problems in schools and where interpretations and analyses are of academic or theoretical interest only. Industry needs a definite industrial eye program incorporating first, a different type of equipment from that used in schools; second, simple practical records; and third, interpretations by medical advisers. One of our large manufacturers has accepted the responsibility of having an instrument constructed which will be released as soon as its intrinsic accuracy and effectiveness have been thoroughly checked.

To present the mass of data which comprises the core of our researches is a tremendous venture, and this can be presented only by graphs. The detail of technique, the exact type of records used, and the reasons for the interpretations which have been worked out will be presented in a later paper.

Figure three illustrates a complete summary of the eye findings in the 16,332 individuals who were tested. The visual defects are divided into five groups, as follows: Acuity defects, 21 per cent; acuity defects uncorrected, 12 per cent; stereopsis defects, 16 per cent; color deficiencies, 5 per cent; and muscle imbalances, 22 per cent.

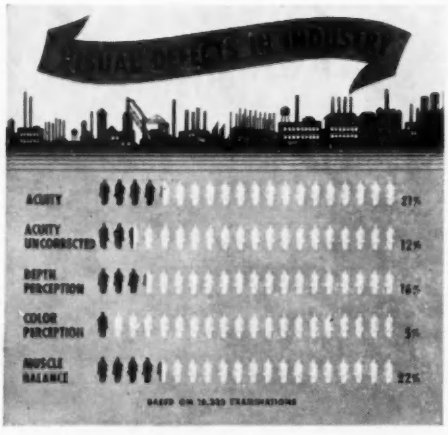


FIG. 3 — *Visual Defects in Industry* — Percentages of individuals in manufacturing industries who fail on various visual performance tests. Figures in black represent the proportions of failures on the various tests among the same group of workmen. Based on 16,332 examinations in various industries in the Calumet area.

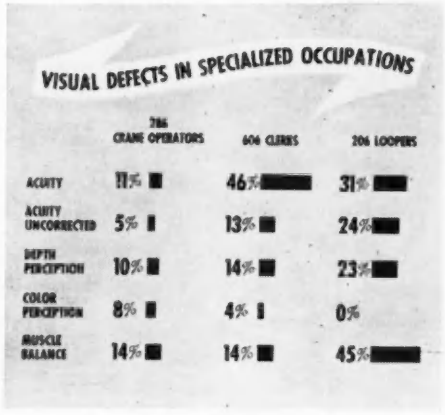


FIG. 4 — *Visual Defects in Specialized Occupations* — Percentages of individuals in different jobs who fail on various visual performance tests. The horizontal black bars represent the comparative percentages of failures. The three jobs represent typical differences in working distances. Percentages of failures in Acuity Uncorrected (even with glasses), Depth Perception, and Muscle Balance shows increases in proportion to the nearness of the work.

Figure four presents an analysis of the five groups presenting defects. Three occupations are listed in which the visual requirements differ markedly. Percentages of failures reveal increases in proportion to the nearness of the work. To find acuity defects and/or a lack of depth perception is of vital importance for crane operators, but of no special concern to manual labor. A marked muscle imbalance in clerical workers has been shown to be detrimental to both their comfort and efficiency, while an ex-

tremely careful study of the five groups presenting defects is essential in hiring individuals for, or analyzing the eye conditions of employees engaged in, looping at a distance of eight inches. For the purposes of industry this type of practical analysis is the basis for deciding where to begin a program by those in charge of personnel where jobs are shifted and insistence on corrective measures is stressed.

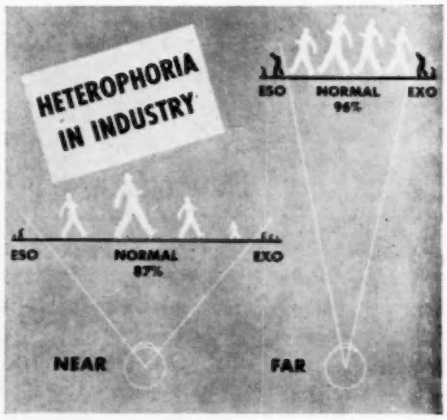


FIG. 5 — *Heterophoria in Industry* — Distribution of muscle balance test findings on distance and near tests. The relative heights of the men indicate the frequency with which heterophorias of different amounts occurred. The black figures represent the proportion of individuals who fell outside the ranges of passing on these tests. These ranges correspond to 3 P.D. of esophoria to 5 P.D. of exophoria on standard tests at distance, and 2 P.D. of esopheria to 8 P.D. of exophoria for near.

In figure five is shown an analysis of the heterophorias found in industry. I have designated as failures those who, in my opinion, have muscle imbalances sufficient to produce an industrial handicap. This includes all who are outside the normal ranges, namely, 3° of esophoria to 5° of exophoria for distance, and 2° of esophoria to 8° of exophoria for near. This is the basis for the statistical complications of defects *found* and not the basis for a program of correction which in the case of phorias is decidedly a question of specific jobs and efficiency.

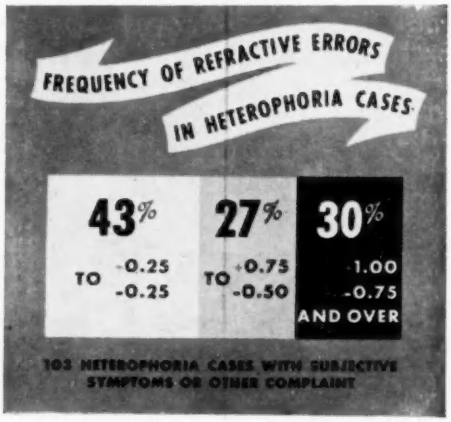


FIG. 6 — *Frequency of Refractive Errors in Heterophoria Cases* — Frequency of refractive errors (determined under cycloplegia) of different amounts among 103 cases of marked muscle imbalance whose visual complaints brought them to the Ophthalmologist's office for help. Seventy per cent of these cases show negligible refractive errors, and an additional 27 per cent show only minor errors.

In figure six is shown a series of 103 cases with definite muscle imbalance where there were subjective symptoms or complaints regarding work. These were refracted under cycloplegia to discover the incidence of refractive errors in cases with marked phorias. It was demonstrated here, and has been demonstrated repatedly since, that among adults with marked heterophorias, refractive errors are negligible in the main, 43 per cent having none and 70 per cent having minor errors. This I feel offsets the careless statement frequently made, "If the refractive error is corrected, usually there is not a problem of muscle imbalance."

Phoria findings for distance and for near, as indicated on the stereoscope, were checked in one plant where 969 persons were employed against *other* methods of measuring muscle imbalances, and the stereoscopic findings were found to be of more than practical accuracy. While the data here is absolute-

ly convincing as to the impracticability of using such methods as the cover test, rotary prism, and Maddox Rod and Maddox Wing test in making eye examinations within an industrial concern, where one is seeking to find applicants' or employees' handicaps, we are postponing publication and discussion of this detailed study.

FIG. 7 — *Visual Defects Needing Correction* — Percentages of individuals in a large industry whose composite *scores* on several visual performance tests indicated serious defects most likely needing immediate attention. Fifteen per cent show urgent need for attention. The insert indicates in total manufacturing industries the number of individuals needing immediate ocular attention as estimated from the percentages disclosed in this study.

Figure seven gives an analysis of serious visual defects which were found and which I believed should justifiably be chosen for correction and be reported to the employee. These comprise about 15 per cent of all employees in a study of 9,115 individuals; or projected into total manufacturing industry alone, there are 1,270,000 serious defects. It is at once quite evident that these percentages are in contrast to actual incidence of defects. Practical considerations demand a certain elasticity of interpretation of what is failure of visual performance for a specific person as compared with the theoretical norm. As an analogy, there is an average stature for man, but unless any individual's height falls below or above a wide range of variation and is related to work requirements, it has no practical significance. So also could further fantasy enter our appraisal of industrial defects if we lost our perspective.

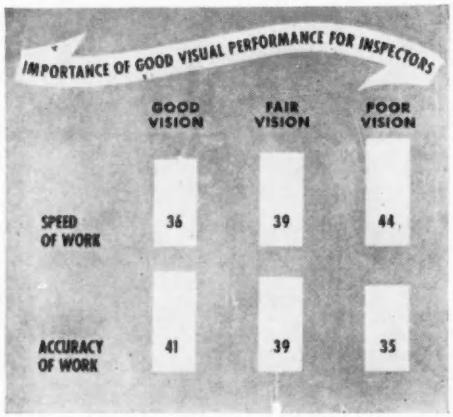


FIG. 8 *(a)* — *The Importance of Good Visual Performance for Inspectors* — Relative speed and accuracy of work done by tin plate inspectors differing in visual performance characteristics. "Good Vision," "Fair Vision," and "Poor Vision" are determined by the number of visual performance tests failed by each inspector. The vertical white bars in the upper level indicate the relative amount of tin plate inspected per unit time. The white bars in the lower level indicate the relative accuracy (reciprocal of the number of mistakes) in sorting the tin plate. Those with poorer vision do more work but do it less accurately. Adapted from a cooperative study with Joseph Tiffin, Ph.D., Purdue University.

Figure eight (a) demonstrates the importance of good visual performance for inspectors. In this study, conducted with the cooperation of Purdue University, it was found that girls with poor vision work faster than those with normal vision because they do not see defects, while accuracy of work is in direct proportion to visual perfection. The upper level of bars indicates the number of sheets of tin plate per unit time, and the lower level of bars indicates the proportion of sheets correctly sorted.

Figure eight (b) indicates how good visual performance also is important for clerical work. The verifying, punching,

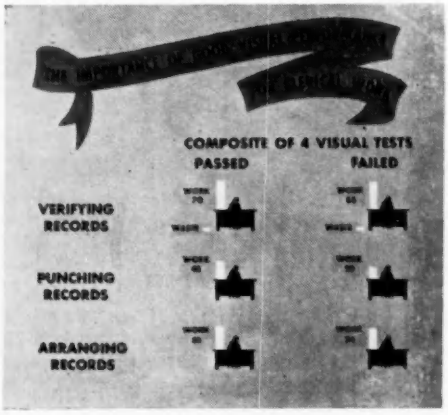


FIG. 8 *(b) — The Importance of Good Visual Performance for Clerical Work* — Relative speed and accuracy of work done by clerks in three jobs involved in modern mechanical accounting systems: The vertical white columns resting on the desks represent the relative amounts of work accomplished. Adapted from a cooperative study with Joseph Tiffin, Ph. D., Purdue University.

and arranging of records was studied statistically, using the composite of four visual tests. This shows volume of work as related to visual aptitudes. The white columns resting on the desks represent the relative amount of work. Professsor Tiffin of Purdue University cooperated with us in making this survey, also.

Figure nine is an analysis of the visual performance which was found in people *applying* for jobs in industry. Such a group offers the greatest potential field of rehabilitation of all, both because of the youth of the majority of applicants, and also because of the urgent physical needs of individuals for qualification in their basic aptitudes, of which visual performance is one. Industry is setting a standard so as to *avoid* hiring individuals who have defects which hamper them in industry.

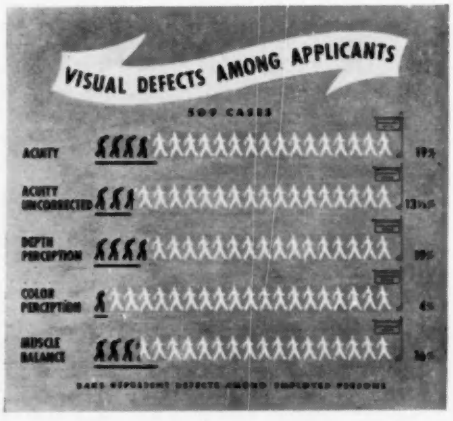


FIG. 9 — *Visual Defects Among Applicants* — Proportion of individuals among applicants for jobs in industry who fail on various visual performance tests. The black figures represent the percentages of individuals in the same group who failed each of the tests. The black bars under these figures indicate the percentages of those already employed in industry on these same tests, as shown in FIG. 3.

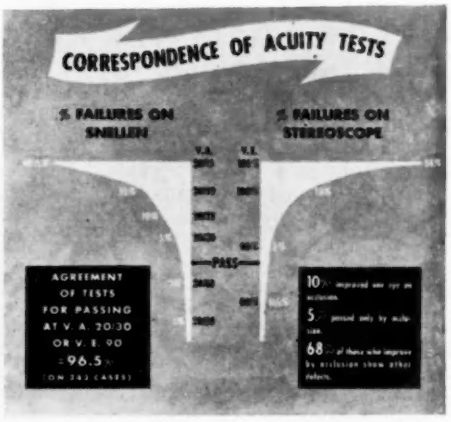


FIG. 10 — *Correspondence of Acuity Tests* — Cumulative percentage of individuals failing at different levels on two acuity tests, the Snellen Chart and the stereoscope test, both of which were given to the same group. The stereoscope test is calibrated according to the A.M.A. percentage rating, which is designated as "visual efficiency" or "V. E." to avoid confusion with the "visual acuity" or "V. A." rating of the Snellen scale. The inserts report supplemental calculations — the occlusion percentages from a series of 2,012 cases.

Figure ten correlates the validity of the tests for acuity recorded by use of the telebinocular and those recorded by use of a properly set up and illuminated Snellen chart. The two tests tally in 96.5 per cent of 342 cases for passing at equivalent levels which are 20/30 (Snellen) or 90 per cent (A.M.A.). The strange phenomena of improvement in acuity by occlusion in a certain percentage of

readings on the telebinocular were studied in 2,102 cases. The graph shows that the vision of 9.9 per cent of all the individuals who were tested improved with occlusion. It also shows that the impaired vision in 67.7 per cent of the cases which improved under occlusion is associated with other visual defects that make binocular vision difficult, for example, faulty stereopsis or marked muscle imbalance. I felt that a very small percentage of visual defects was related to the psychic factor of instrument convergence and even this has been eliminated, I believe, by the new instrument.

The Department of Applied Psychology at Purdue University requested and used our data on one group of 9,168 employees, adding to the data various measures of ability and frequency of accident. This brilliant study and complete statistical analysis will constitute not only the most comprehensive study of vision (the range of which is roughly indicated in figure eleven), but also a study of phorias, stereopsis, and color. In addition it will be the most complete study of merit ratings and accidents versus visual performance ever attempted in any industry. When this data is published, it may challenge some empirical concepts of norms, or it may scientifically substantiate them, for example, incidence of 20/15 as indicating a norm in the better of the two eyes rather than 20/20. However, I am not certain of this.

A special study was made of visual performance at a working distance of eight inches from the eyes such as is used by loopers in the hosiery industry. This study also is not yet ready for publication because it opens up a field of work pioneer in character and totally unexplored. The obvious difficulties in production and efficiency as well as probabilities of binocular breakdown brought to us at once the possibility of occupational corrections, especially adapted to the abnormal working distance of eight inches, as well as the need of entirely new standards whereby to judge applicants in this industry.

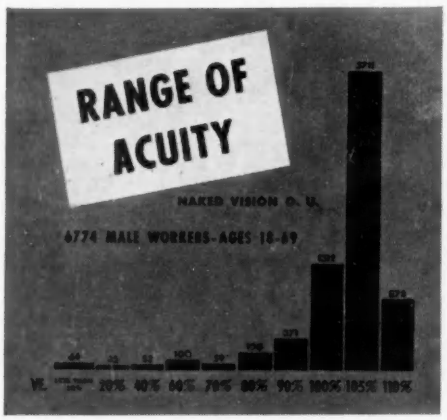


FIG. 11 — *Range of Acuity* — Frequency of acuity scores at different levels, naked vision O. A., on the A.M.A. percentage scale.

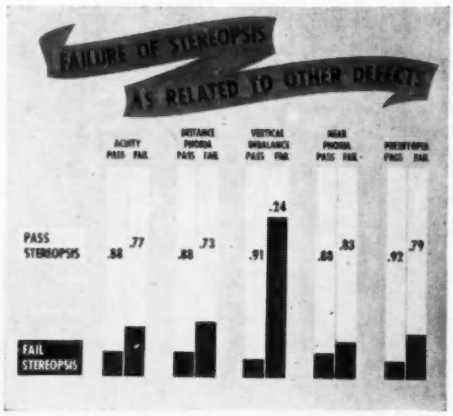


FIG. 12 — *Failure of Stereopsis as Related to Other Defects* — Percentages of individuals, of those passing and failing respectively on five other tests, who also pass on the stereopsis (depth perception) test.

We did not do any new investigative work on stereopsis other than to note its relationship to other defects such as acuity, distance phorias, vertical imbalances, near phorias, and presbyopia, as shown in figure twelve. (Notice especially the close relationship to incidence

of imbalances.) However, a project designed to determine the practical value of stereopsis beyond 100 to 150 feet has been launched in a steel mill equipped with cranes whose span is great enough.

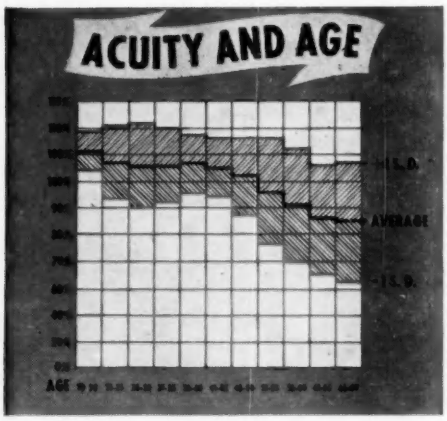


FIG. 13 — *Acuity and Age* — Average acuity and average range of acuity in respect to age. The vertical scale represents acuity (naked vision O. A.) in A.M.A. per cent notation.

Figure thirteen shows a study of the relationship between acuity and age. The average acuity drops consistently with increasing age and with a spread in deviation from average.

The details and varieties of follow-up programs were worked out with the management, both with regard to reporting defects to individuals and to the types of correction required for individuals. The situations with which we were confronted included focusing attention on special groups, such as inspectors and assorters in steel, or loopers in hosiery, giving impetus to safety departments toward improved types of corrective goggles and to more accurate records of causes of accidents, setting up higher but fairer and more practical standards for new employees by conference with company doctors and insurance companies, working out a visual program for any industry needing advice or guidance, and studying problems pertaining to truck driving, traffic, and accidents. However, it has been impossible to touch on all of these matters today. I can only hope that by presenting this discussion of a *few* excursions into a vast unexplored world of service open to and increasingly demanded of Ophthalmologists who practice in industrial communities or who are retained as ophthalmological advisers in industrial concerns, I have presented some helpful information. This research has been to me a liberal education in the field of industry. It is quite obvious that the Ophthalmologist of today will be asked to participate more and more frequently in the affairs of industry if he learns to take into consideration factors which are not necessarily important in dealing with sick patients or with office examinations.

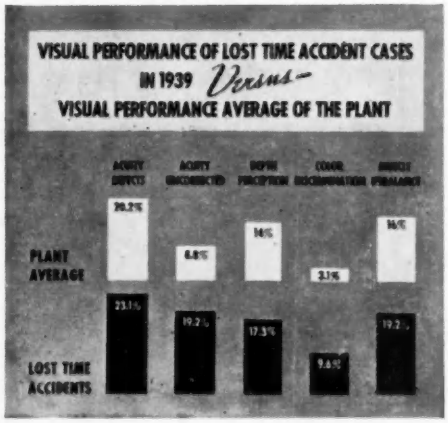

VISUAL PERFORMANCE OF LOST TIME ACCIDENT CASES
IN 1939 Versus
VISUAL PERFORMANCE AVERAGE OF THE PLANT
PLANT AVERAGE
LOST TIME ACCIDENTS

FIG. 14 — Percentage of failures on various visual performance tests of a group of workers who had lost time from accidents in 1939 in comparison with corresponding percentages of a cross section of all workers in the same plant.

In conclusion, the special facts which I would like to impress are: First, the technique of binocular testing of visual performance in industry has now thoroughly been tested and investigated. Many improvements and safeguards to accuracy have been worked out, and an instrument in itself very simple has been

adapted to the complex needs of industry. Second, industry needs *much* more information about an employee's eyes than it has been receiving at the time the employee is checked when being hired, or when the employee's eyes are checked in the Ophthalmologist's office. It behooves each of us to meet this need. Third, while surveys and visual performance tests are actually administered to better advantage by the trained lay expert, the program of a survey or the supervision of admission standards and the selection of employees for further examinations should be under the supervision of an Ophthalmologist, preferably one who has studied the many angles of this special field. Fourth, an invaluable contribution could be rendered by the Academy to the industries of America and to the many Ophthalmologists seeking specific, practical, and immediate information. This contribution would consist of the immediate publication of a handbook on industrial problems pertaining to vision, which could be worked out by a joint committee sponsored by the Academy. This committee would include as advisers, leaders in training departments of industries, authorities in industrial and trade education departments of universities, and representatives from government groups now setting up various vast training programs. Industry everywhere is coming to us for advice and assistance. Let us be intelligently informed and ready to cooperate by applying our clinical knowledge in ways that industry can use to advantage.

DISCUSSION

JOHN B. HITZ, M.D., Milwaukee: First, I should like to compliment Doctor Kuhn for performing an excellent job concerning an important phase of clinical research. The graphic, almost dramatic, method of presentation will leave most of us with a clear and permanent impression of her findings. The very magnitude of the problem would make many of us turn our tails and run in the opposite direction.

I believe Doctor Kuhn has impressed us with the necessity of actually visiting the manufacturing plants in order to obtain first-hand knowledge of working conditions if we are to be of service in this phase of Industrial Ophthalmology. I was interested enough in the study to visit Doctor Kuhn and to see for myself the various problems encountered. It is one thing to be told that employees in the hosiery industry work at looping which is done eight inches distant from their eyes, and another to see 200 girls threading stitches on rows of needles considerably less than 1 mm. apart, many of them inclining their heads backward in order to obtain maximum infraduction and hence maximum convergence.

I believe it detracts somewhat from the force of Doctor Kuhn's paper to omit detailed explanation regarding the tests and techniques used. The numerous tests used, I understand, is a modification of Bett's tests, designed for testing school children, with considerable simplification and readjustment of the criteria for passing the test.

Stereoscope technique has several advantages in this situation which are not so evident in school tests. The principal ones are portability of the instrument, the small amount of space required for it, and uniformity of illumination. Its disadvantages are that the muscle balance in stereopsis tests do not, in my opinion, correlate well with the more generally known and accepted tests. Absence of stereopsis, as measured on the stereoscope, does not necessarily indicate inadequate depth of perception, as measured on an instrument such as the Howard Dolman apparatus.

I do feel, however, that these disadvantages in the stereoscope do not invalidate the findings in general presented in this paper. Further comparative studies with other methods of testing visual performance are definitely in order. These should be done on a sufficiently large scale to be of real proof, preferably done by three or four independent investigators.

Any mass testing of this sort must obviously be turned over to lay technicians until such a time as the graduate schools are able to turn out enough trained Ophthalmologists to take over all visual testing, both in industry and in the National school systems.

Any group of visual tests, however, is not foolproof, and in order to obtain accurate results, *trained* technicians are necessary. It is my opinion that no one is competent to make accurate visual tests, tests for muscle

balances, et cetera, regardless of the apparatus used, with less than three months full time training. If the programs of visual testing in schools and industries are to mean anything in the future, training schools should be established for nurses in industrial and public health and, when necessary, for teachers.

It is papers such as this which will sell industry on the fact that industrial safety and efficiency depend, at least in part, on visual performance.

CONRAD BERENS, M.D., New York, New York: The problem of visual defects in industry is so vast and so important, especially in this time of National danger, that we are indeed fortunate in hearing a report of Doctor Kuhn's personal experience in attacking this work. Her statement that there is little knowledge concerning visual performance in industry is unfortunately true. This problem is much like that of visual fatigue. At the end of a long conference on visual fatigue, Miles summed up the situation by stating that, "Socially we find ourselves on familar territory in talking about this experience of visual fatigue, but scientifically we seem to be lost in the woods."

It is pointed out that little attention has been paid to standards for specific jobs and the difficulty of making these practical and flexible. Those, who have worked with standards for aviation or any other comparatively recently developed service, appreciate how difficult it is to make these standards practical and sufficiently flexible so that valuable men will not be excluded from services, especially when the actual testing is done by men of limited experience in the special field.

In making these studies, Doctor Kuhn has used the telebinocular. The study of 100 patients with the telebinocular leads me to believe that she made a wise choice, in spite of the criticism which has been made of these tests. I agree with her that there are needed changes, not only in the instrument itself but also in the material to be used, with an instrument of this type. Therefore, I am glad that she is preparing to give us something better adapted to the needs of industry.

Doctor Kuhn mentioned "duction" and I wonder whether she also studied the near point of convergence, which, in my opinion, often gives us important data concerning the use of the eyes at the near point.

Another point in her examination is that she used laymen; she believes that perhaps they do this work better than Ophthalmologists. Having used sergeants in the Army to make tests and having trained technicians as Ophthalmologist's assistants, I agree with her that this is a wise policy. Moreover, because of the routine nature of the work, the tests even may be performed more accurately in the majority of instances than if they were made by Ophthalmologists. Naturally, medical guidance and control must be insisted upon. Further, the employment of lay assistants to do this work, under the guidance of an Ophthalmologist, would make it financially feasible for many industrial organizations to introduce routine eye examinations.

I also agree with her criticisms of the tests ordinarily employed and how inadequate they are. It is obvious that color deficiencies, with tests ordinarily used, are not graded for "job requirements." Group color vision tests would be valuable and I[2] have proposed a method of group testing which would save time.

I am sure that Doctor Kuhn will agree that the individual's ability to overcome heterophoria is more important than the amount of imbalance present, but I agree that the muscle balance should not be neglected. In addition, for persons who must use their eyes at the near point for long periods of time, I believe the eyes should be tested for fatigue of accommodation and possibly for fatigue of convergence.

There is no question but that for many accupations, stereopsis is important and more attention should be paid to the distance at which the work is to be performed. If at six meters, I prefer the six meter recording stereoscope which includes reaction time; if at the middle distance, a modification of the Davidson Perlia test[1] is valuable; if at the near point, the Davidson modification of the Perlia test is more useful.

Doctor Kuhn's analysis of visual performance in applicants for jobs in industry is particularly interesting; I would like to ask her whether the important problem of the rehabilitation of these applicants has been attacked. We found that we often were able to help aviators, who could not meet requirements either before or after entrance in the service. This is where the great field of orthoptic work should find an important niche.

The positive correlation of visual performance with accuracy of work is encouraging for future selection problems. The fact that speed that leads to inaccuracy is often associated with visual defects is an important lesson for industry. I would like to know whether Doctor Kuhn found that greater speed was

obtained in certain tasks with monocular vision than with binocular vision. The question is asked because monocular reading is often more rapid than binocular reading, and books have been published in small print to be read with magnification before one eye. I also would like to ask Doctor Kuhn whether she has used monocular magnified vision as compared to binocular vision. The problem of working within, or close to, the average near point of accommodation is much like that of older ophthalmic surgeons who often find prisms combined with strong plus lenses most useful.

In studying visual acuity, we also found that, as a rule, visual acuity with the telebinocular approximated fairly closely the acuity found with the Snellen charts, and I agree that the disadvantages of the usual Snellen test are great. Because of deception used by aviators, we used the Ives test for the accurate determination of visual acuity. A visual acuity test for group examinations was presented before the Section on Ophthalmology of the American Medical Association.[2]

Figures showing that 10 per cent of individuals show improvement in vision with occlusion and the correlation of this finding with other visual defects, which made binocular vision difficult, are to my mind the most important findings in this splendid study.

Another part of the study, which impressed me greatly, was the report concerning muscular imbalance. I hope that the statement, "If the refractive error is corrected, usually there is not a problem of muscle imbalance," will settle the question forever.

It is gratifying to know that follow-up programs are being worked out because in clinical work we know how important follow-up procedures are in obtaining worthwhile data and in seeing that defects are eliminated or corrected.

It is unfortunate that time did not permit Doctor Kuhn to give us more data concerning many of the important problems, which she has brought to our attention, such as the question of goggles, traffic problems, and accidents. However, I am sure that she has stimulated each one of us to place more importance on binocular testing of visual performance and that we will consider more carefully the type of examination we recommend for industry.

Finally, I hope that she will present a resolution to the Academy concerning the preparation of a handbook covering the various phases of this pressing problem and that the new text soon will be available.

1. Berens, C.: A modified Perlia test for depth perception at middle distance, Tr. Sect. Ophth., A. M. A., 1939, p. 469.
2. Berens, C.: Visual acuity test applicable to testing large groups of subjects, Tr. Sect. Ophth., A. M. A., 1939, p. 472.

HARRY S. GRADLE, M.D., Chicago: The value of a visual survey of any magnitude lies less in the discovery of the number of visual defects than in the number of corrections that can be effected. Consequently, I wish to present with great pride a short analysis of the program now being carried out in the State of Illinois.

About three years ago the Works Progress Administration initiated a program of visual survey and correction among the children of the primary schools. The Illinois Society for the Prevention of Blindness was asked to direct and supervise the project which is still under way. The State was apportioned into six downstate and one Chicago district. Defects revealed by the survey were classified as: *1X* (vision of *20/40* or better), *2X* (vision between *20/40* and *20/70*), and 3X (vision worse than *20/70*). The parents of all children with defective vision were notified by mail or personal call of the existence of the reduced vision, and every effort was made to bring the child to an Ophthalmologist for correction of the vision.

The following is a brief statistical analysis of the work in the seven districts up to June 1, 1940:

DISTRICT ONE

Normal Vision		54,016	90.54%
1X		2,894	4.85%
2X		2,290	3.84%
3X		460	.77%
Total		59,660	100.00%
Schools tested	1,211		
1X Cases		2,894	
1X Corrections		733	
Percentage			25.33
2X Cases		2,290	
2X Corrections		508	
Percentage			22.18
3X Cases		460	
3X Corrections		169	
Percentage			36.74
Total X Cases		5,644	
Total X Corrections		1,410	
Percentage			24.48

Tested 119,213 children to June 1, 1940

DISTRICT TWO

Normal Vision	37,554	92. 7%
1X	1,661	4. %
2X	1,072	1.7 %
3X	260	.6 %
Total	40,547	100.00%
Schools tested 394		
1X Cases	1,661	
1X Corrections	356	
Percentage		21.4
2X Cases	1,072	
2X Corrections	289	
Percentage		26.9
3X Cases	260	
3X Corrections	99	
Percentage		34.2
Total X Cases	2,993	
Total X Corrections	744	
Percentage		24.8
Tested 75,359 children to June 1, 1940		

DISTRICT THREE

Normal Vision	9,808	89.36%
1X	637	5.83%
2X	464	4.22%
3X	65	.59%
Total	10,974	100.00%
Schools tested 73		
1X Cases	637	
1X Corrections	153	
Percentage		24.02
2X Cases	464	
2X Corrections	236	
Percentage		50.86
3X Cases	65	
3X Corrections	86	
Percentage		132.30
46 of these corrections from school year 1938-39		
Total X Cases	1,166	
Total X Corrections	475	
Percentage		40.73
Tested 20,965 children to June 1, 1940		

DISTRICT FOUR

Normal Vision	3,466	91.07%
1X	176	4.62%
2X	136	3.57%
3X	28	.74%
Total	3,806	100.00%
Schools tested 145		
1X Cases	176	
1X Corrections	71	
Percentage		40.34
2X Cases	136	
2X Corrections	91	
Percentage		66.91
3X Cases	28	
3X Corrections	25	
Percentage		89.28
Total X Cases	340	
Total X Corrections	187	
Percentage		55.00
Tested 7,136 children to June 1, 1940		

DISTRICT FIVE

Normal Vision	12,560	90.8 %
1X Cases	795	5.8 %
2X Cases	391	2.8 %
3X Cases	82	.6 %
Total	13,828	100 %
Schools tested 339		
1X Cases	795	
1X Corrections	162	
Percentage		20.25
2X Cases	391	
2X Corrections	127	
Percentage		32.48
3X Cases	82	
3X Corrections	35	
Percentage		42.68
Total X Cases	1,268	
Total Corrections	324	
Percentage		26.3
Tested 24,303 children to June 1, 1940		

DISTRICT SIX

Normal Vision	26,651	92.80%
1X	1,053	3.66%
2X	806	2.81%
3X	221	.73%
Total	28,731	100.00%
Schools tested 578		
1X Cases	1,053	
1X Corrections	152	
Percentage		33.86
2X Cases	806	
2X Corrections	166	
Percentage		36.97
3X Cases	221	
3X Corrections	131	
Percentage		29.17
Total X Cases	2,080	
Total X Corrections	449	
Percentage		21.59
Tested 54,051 children to June 1, 1940		

DISTRICT SEVEN

Normal Vision	195,003	89.44%
1X	8,767	4.02%
2X	12,392	5.69%
3X	1,851	.85%
Total	218,013	100.00%
Schools tested 297		
1X Cases	8,767	
1X Corrections	1,709	
Percentage		19.49
2X Cases	12,392	
2X Corrections	5,240	
Percentage		42.49

3X Cases	1,851	
3X Corrections	1,047	
Percentage		56.56
Total X Cases	23,010	
Total X Corrections	7,996	
Percentage		34.75

Tested 74,532 children to June 21, 1940

In summary, visual tests were made of 375,559 unselected children from 3,037 primary schools throughout the State of Illinois. 90.96 per cent were found to have normal vision; 4.69 per cent had vision between 20/20 and 20/40; 3.65 per cent were found to have vision between 20/40 and 20/70; and 0.70 per cent had a visual acuity of less than 20/70. The number of visual deficiencies which were corrected varied from 25 per cent to 89 per cent, according to the locality, with an average of around 38 per cent. There was but little variation in the percentages of visual defects found in children from rural districts as compared with those from cities. It was striking that a greater percentage of corrections was obtained in children with the higher visual defects, probably because of more intensive efforts on the part of the workers.

HEDWIG S. KUHN, M.D., Hammond, Indiana: First of all, the criticism of our not showing the actual technique and program is quite justifiable. It could not be incorporated in the time allotted for this presentation, but it is available to anyone who is interested.

Doctor Hitz' comment on stereopsis tests and their inaccuracy on the basis of the binocular set-up is theoretically and absolutely correct, but all of these tests were conducted in such a manner that each employee would not need to be away from his job for more than 10 minutes. When making tests on 10,000 employees who are working in a steel plant that is operating on full schedule, there is not time enough to do each one of them absolutely perfectly. The tester's responsibility is reduced to discovering those employees who have no depth perception and its importance to the job. The employee is not dismissed because of that, but if he is found to lack stereopsis essential for his job, he is checked with the finer techniques of stereopsis, as Doctor Hitz has suggested.

Regarding Doctor Berens' comment in which he asks if we did any monocular work, I admit that we did not do so at this time. We would have liked to, and intend to, do this and many other features.

We did check the point of convergence in all employees who were engaged in close work. Each industry with which we have worked has set up a rehabilitation program, differing in accordance with the industry's policies, their possibilities, and the type of work required. This is especially important in the case of applicants for near work who have phorias that are handicapping, just as in aviation applicants with phorias are merely requested to have phorias corrected instead of seeking another job.

Mention should be made here regarding the unions. In our section of the country that is very pertinent to the subject. Fortunately, the unions were both cooperative and understanding. They realized the correlation between the merits of physical perfection and those of seniority rights. In one plant the survey actually was the basis whereby the company was able to sign a contract with the union which recognized physical attributes of various types that would affect promotion in preference to seniority rights, where advancement in a job depended upon the aptitude of the worker. They had not been able to do this before the survey had been made and before the function of the survey had been demonstrated to them.

Comparing Doctor Gradle's survey which reveals 4 per cent of school children with defects and our survey which reveals 15 to 20 per cent of individuals in industry with defects illustrates another sideline, that of lessening the ultimate number of defects present in adults by correcting those existing in children during the early stage.

I would like to show you a safety record, because I believe Doctor Hitz was not prepared to tell you what it illustrates. This is the first time that we have been able to find in the literature, from individuals, or from industries where there is direct correlation between accidents, time off because of accidents, and visual defects (Fig. 14). You will notice that the correlation is most marked in the cases where the acuity has not been corrected. There are twice as many accidents causing loss of time from work in the group of cases with uncorrected acuity than in the group of cases with color blindness. This survey was made in a plant employing over 15,000 individuals. Eighty per cent of the accidents causing loss of time for the year 1939 are the basis of this particular correlation.

Scientific Instruments

THE CARDINAL ANGLOMETER

EMANUEL KRIMSKY, M.D.
NEW YORK

THE CARDINAL ANGLOMETER is, as its name implies, an instrument for the measurement of the status of the ocular muscles not only in the primary position, but in any selective direction of gaze at the distance of 13 inches from the eyes. In addition, this instrument is intended to measure the visual or binocular status for these respective positions of gaze.

The instrument permits one to carry out tests according to established principles, but also by careful control and observation of the movements of the eyes. In this calibrated instrument due provision has been made for:

1. Fixation of the head both in the erect and tilted positions.
2. Controlled study of positions and movements of the eyes, and of image responses so as to measure true and anomalous projections.
3. Studies of binocular status in definite and selective positions of gaze.
4. Adjustment of prism or filter holder to head-rest so as to leave hands free to carry out other operations.
5. Ready selection of bright transparent targets of different sizes, intensities, or colors, as well as flashers for cases of amblyopia or suppression.

The meachanical features of this instrument include:

1. An adjustable head-rest for erect or tilted positions.
2. A graduated arc, pivoted on sides.
3. Calibrated light carrier —
   a. Can be moved 10 degrees up or down and permits a maximum vertical displacement of 20° between two targets without supplementary prisms. (It is to be noted that

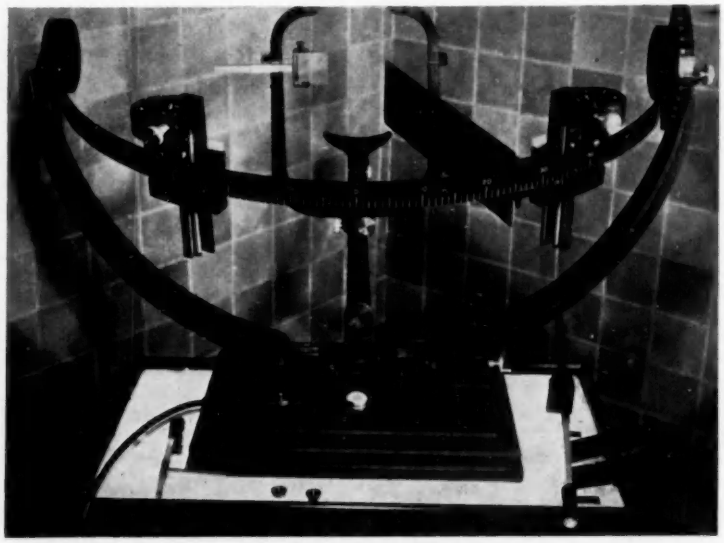


FIG. 1 — The Cardinal Anglometer

calibrations on this instrument are in arc degrees.)
   b. Marker for .75° and 2.5° targets respectively.
   c. Flasher.
   d. Selection of transparencies.
4. Indicator for vertical arc displacement to record the amount of upward or downward gaze.
5. Movable base support for head-rest.
6. Adjustable prism and filter holders.
7. Convergence rule attachment.
8. Removable septum.

The anglometer permits such measurements as:

1. Angle gamma.
2. Phorias in any selective positions of gaze.
3. Type and amount of manifest squint both as regards vertical or horizontal deviations in any position.
4. Field of monocular deviations in any position.
5. Field of binocular fixation.
6. Field of binocular fixation, as well as diplopia fields.
7. Amount and type of diplopia in different fields.
8. Vertical ductions (vergences) in their minute components. Right superduction, subduction, etc., as well as breaking and recovery points.
9. Convergent near-point — symmetric and asymmetric as well as maintenance time.
10. True and anomalous projections.
11. Binocular status in relation to head tilt.
12. Primary and secondary deviations in case of paralytic squint.
13. Amount of lateral ductions — although less satisfactory than with the phorometric stereoscope.

The anglometer is not used for visual field studies because mechanically the arc is pivoted on the sides rather than on a fixed center.

FIG. 2 — Showing the use of supplementary prisms in cases of esotropia. In marked esotropia the monocular fixation method without prisms is used.

While the instrument lends itself to measurement by such familiar methods as the Red-Green Test, or Simple Prisms, I have found the Septum or Modified Screen Method the most satisfactory in selected cases, because it permits careful observation of eyes at all times and provides readings comparable to those obtained with prisms and cover. Hence the Septum Method serves as a quantitative screen test.

My method of examination includes a routine preliminary study including prism tests for 20 feet.

With the anglometer, adapted to a fixed distance of 13 inches, I resort to a qualitative screen test at selective positions of gaze and plot findings on a graph. The methods I select are:

A. Septum alone — for exophoria or exotropia.
B. Septum and supplementary base-out prisms — for esophoria or moderate esotropia.
C. Monocular fixation — for marked esotropia.
D. False projection — for paralytic esotropia.

These methods, as well as the underlying principles, were described in detail in my recent exhibit, and will form the basis for a separate report.

Both the anglometer and my phorometric stereoscope employ the principle of the Septum Method. There are, however, certain differences between the anglometer and the stereoscope or synoptophore:

FIG. 3 — Showing the targets set to an angle corresponding to 45° exotropia, and 4° L.H. In this case there was superposition of images, or true projection.

1. The anglometer limits the examiner to a fixed distance of 13 inches. The stereoscope with its correcting lenses and variable viewing distances permits one to study binocular status at different accommodative ranges.
2. The anglometer permits a study of the peripheral motor fields. The stereoscope limits one to a study of the central fields.
3. The stereoscope is more suitable for study and measurements of lateral duction in their minute components for near and for far; for the study of true and anomalous projections; for stereopsis; and for training.
4. Both the stereoscope and the anglometer offer distinct although complimentary fields for study.

REFERENCES

1. Krimsky, E.: The stereoscope in theory and practice, Brit. J. Ophth. 21:161-197 (April) 1937.
2. Krimsky, E.: Some newer developments in precision - type stereoscopes, Arch. Ophth. 19:394-402 (March) 1938.

The author is grateful to Dr. Walter B. Lancaster for suggesting in the interests of proper word derivation the term "Cardinal Goniometer"; and to Dr. Percy Fridenberg for recommending the title "Cardinal Angulometer."

A NEW MODEL OF GONIOSCOPE

MANUEL URIBE TRONCOSO, M.D.
NEW YORK

IN 1925, I devised an instrument for the examination of the angle of the anterior chamber which I called the *gonioscope*. This instrument is a microscope giving erect images from ×13 to ×20. To it is attached a periscope and an illuminating system which gives a powerful illumination area. A new hemispherical contact glass without any cavity (Glass C. Koeppe) allows an examination of the angle all around the limbus by turning the periscope. The microscope gives a good image of the sinus of the chamber, deeply and on the same side on which the observer stands, a feature which is important in glaucoma cases. However, the use of a prism made the indirect images a little difficult to focus and required from the observer a special training. For this reason the gonioscope did not have the popularity it deserved.

To avoid this drawback, I have devised a new model of gonioscope in which the examination of the angle is made laterally and the image appears on the opposite side of the observer, thus making the observation easy. However,

This instrument is made by Mr. K. Larkin, 635 West 165th Street, New York, N. Y.

this method requires that the operator move around to see all parts of the inner limbus in succession.

The new gonioscope is a microscope which gives an erect image and magnifications from ×15 to ×40. It carries a powerful source of illumination which consists of a 6 volt, 4.5 candle power lamp and a special condenser system. By moving the lamp inside the tube, a brilliant round or a slit shaped area is obtained. The illuminating system is fixed at an angle and can be moved up and down to adjust the area of light to the field of examination when the objectives are changed.

With a direct lateral view of the angle as given by the new gonioscope, the ciliary body band over the edge of the iris will be narrower than with the old gonioscope. To examine the sinus of the angle deeply, the observer will have to raise gradually his plane of examination from the surface of the iris by moving the gonioscope towards the top of the contact glass until the image blurs.

In difficult cases, the operator may use a higher magnification to examine the surface and upper limit (Schwalbe line) of the trabecular zone. In glaucoma, he may thus determine if the iris edge is separated from the corneal wall and the

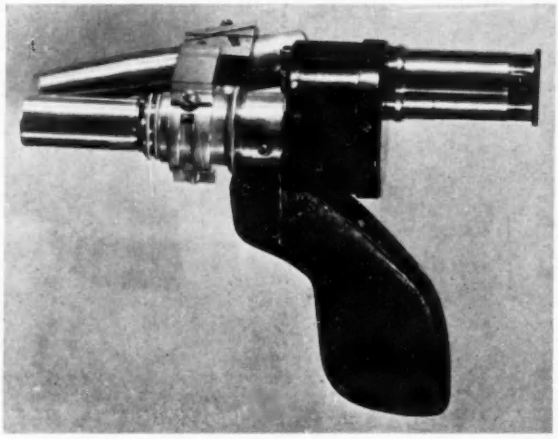


FIG. 1 — Uribe Troncoso's Monocular Gonioscope

I have made this instrument monocular to keep it as handy as the ordinary ophthalmoscope and assure a lower price to the physician. A binocular field is not so important in the observation of the angle, as usually we have only two planes to consider: first, the last roll or edge of the iris, and second, the corneoscleral wall.

However, for those who desire a binocular image the gonioscope may be provided with another eye piece. Unfortunately it will also increase the size and weight, and the price will be higher.

sinus obliterated; that is if there is a peripheral synechia.

To the eye piece of this instrument a micrometer scale can be added. This may be of use to determine the size of lesions or tumors in the angle and if they increase in volume or not after repeated examinations.

A NEW LUCITE CONTACT GLASS

The gonioscopic contact glass has a hemispherical curvature which makes it thick and heavy. Its price is high and if it slips from the fingers and falls down,

it is ordinarily a total loss. To avoid these disadvantages, I have used the new plastic material *lucite* instead of glass. This new contact glass has the same external curvature as the old one, but it is ground inside to form a shell, which makes it lighter. Besides it is unbreakable and its price is low. It has, however, the disadvantage of being a little less transparent than true glass and gives less magnification, but with the powerful illumination and magnifications of the new gonioscope, these inconveniences are overcome and the images are very clear.

After applying it upon the cornea, its concavity is filled with water by means of a syringe and a curved lacrimal needle or with an anterior chamber irrigator.

EALES' DISEASE, PROBABLY TUBERCULOUS PERIPHLEBITIS:

Presentation of Clinical and Histopathological Aspects of a Case

EDMUND B. SPAETH, M.D.
PHILADELPHIA
and
PERCE DE LONG, M.D.
PHILADELPHIA
BY INVITATION

THE CASE we are reporting represents one of progressive, recurrent retinal hemorrhages associated with progressive periphlebitis of a very high degree, signs of chronic iridocyclitis in the anterior segment, practically complete retinal separation, a hole in the macula, recurrent hemorrhages into the anterior chamber, and a high degree of secondary glaucoma, for which enucleation was finally necessary. The progress of the disease covered a period of slightly more than ten years, and the patient was under our medical observation for over eight years. Following enucleation, the eye was serially sectioned. The pathological findings are presented in detail, and they correlate completely with the clinical findings observed in the fundus.

No attempt is made herein to discuss historically recurrent intra-ocular hemorrhage with progressive periphlebitis, nor does it seem necessary, considering the purpose of this presentation, to enter into any discussion regarding differential diagnosis. From the standpoint of etiology, the case was so thoroughly and exhaustively studied as to focal infection, calcium deficiency, blood serology, blood coagulation and precipitation time, kidney pathology, and possible intracranial pathology that these studies essentially limited the differential diagnosis.

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6-10, 1940, Cleveland, Ohio.

Wills Eye Hospital, Philadelphia, Pennsylvania

The general medical examination revealed one devitalized tooth, which was extracted, slight injection of the pharyngeal wall with hyperplasia of the lymph follicles, and slightly enlarged and cryptic tonsils, for which tonsillectomy was performed. The cardiovascular-renal system was normal throughout. Examination of the lungs revealed evidence of fibrosis posteriorly on the right side from the external portion of the hilus to the upper half of the lobe, and on the left side from the external portion of the hilus to the apex. There were no rales, and fluoroscopic examination of the chest and films of the chest revealed apical fibrosis.

The internist's clinical diagnosis was: Underweight (ten pounds); Chronic Pulmonary Fibrosis (quiescent).

The history of the case, prior to our examination, was as follows: In 1929, the patient had an acute impairment of vision in the right eye, for which he consulted his physician. It occurred soon after a period of great physical activity in soccer, and the physician assumed that the impairment in vision was a result of this. The patient was reassured, and he sought no further medical advice at that time. A year later, at which time the vision in the right eye had been satisfactory for eight months, he suffered another attack of acute visual impairment. He then consulted an oculist who informed him that he had had a hemorrhage in the eye and that he should

"forget it, it would disappear spontaneously, and he should not be concerned." Vision failed to return this time, however, to the degree of acuity that he had had prior to the second attack. A year later, he had another episode of acute impairment of vision, and this time the vision was diminished to the ability to count fingers only. He returned to the oculist whom he had consulted previously, who informed him that "he had had another hemorrhage in the eye, which probably was caused by injury." The oculist stated that there was nothing to do about it, although he did prescribe some medication to be taken orally. However, vision failed to return to a degree greater than the ability to read newspaper type.

At this time, the patient was 31 years of age, and although he was employed as a cost accountant, he derived much physical exercise from sports. The past history was negative, as far as the patient knew, except for scarlet fever at the age of 12. For the five years previously his weight had varied no more than five pounds. He was six feet, one inch tall and weighed 162 pounds.

The patient first consulted us on June 2, 1932, at which time there had been another abrupt, acute onset of impaired vision. This time it was accompanied by a taut sensation in the eye, from which he was relieved only when he kept the eye closed. He was tired constantly. The vision in the right eye was 3/150, eccentric, with correction. The vision in the left eye was 6/5. There was a moderate degree of bilateral, chronic, catarrhal conjunctivitis, which was more marked in the right eye. The tension was 18 and 20 mm. Hg., Schiotz, respectively. The pupils were round, central, and equal, O. D. the same size as O. S., both reacting equally and fairly promptly to all stimuli. The field of vision in the left eye was normal. The field of vision in the right eye was as illustrated in figure 1. Slit lamp examination of the right eye with the pupil dilated revealed no synechiae, the anterior surface of the cornea appeared to be normal and healthy, and there was no evidence of descemitis (even with the high power — however, the beam was very faintly relucent in the anterior chamber). Comparing the texture, color, and structure of the irides, there seemed to be the least bit of dull depigmentation of the brown iris of the right eye. Examination of the right fundus revealed many fine floating vitre-

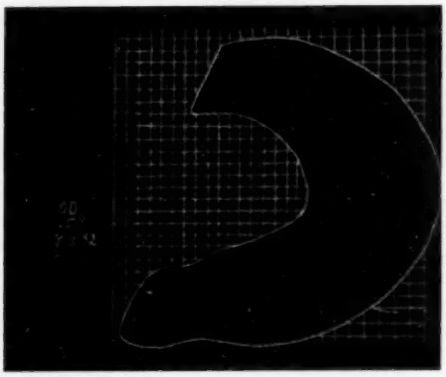


FIG. 1 — The right field of vision shortly after admission.

ous opacities. The disc was somewhat hyperemic. Along the outer margin of the inferior temporal vein, extending from about 6 disc diameters from the nerve head, was a darkish, flame-shaped hemorrhage as seen in figure 2, which followed the vessel almost to the periphery. There was a high degree of peculiar ensheathing perivasculitis of the inferior nasal vein. This was also present on the inferior nasal artery and on the terminals of the superior nasal artery and vein. There were a few fine white spots scattered about in the macula which was somewhat indistinct and seemed to be slightly elevated. Faintly outlined radial lines were present (not a macular star), extending from the macula toward the nerve head in that region of the retina between the temporal margin of the disc

and the nasal portion of the macular region. The periphery of the retina was seen quite distinctly and, except for the vessels, seemed to be normal. The degree and amount of fundus pathology hardly seemed consistent with the high degree of impairment of visual acuity. With the red free light, however, one could see compared with that usually considered within normal limits. There were no changes in the arteries whatsoever, except in some of the various smaller arterioles just within the threshold of visibility with the ophthalmoscope. They seemed to be considerably more tortuous than one would consider normal.

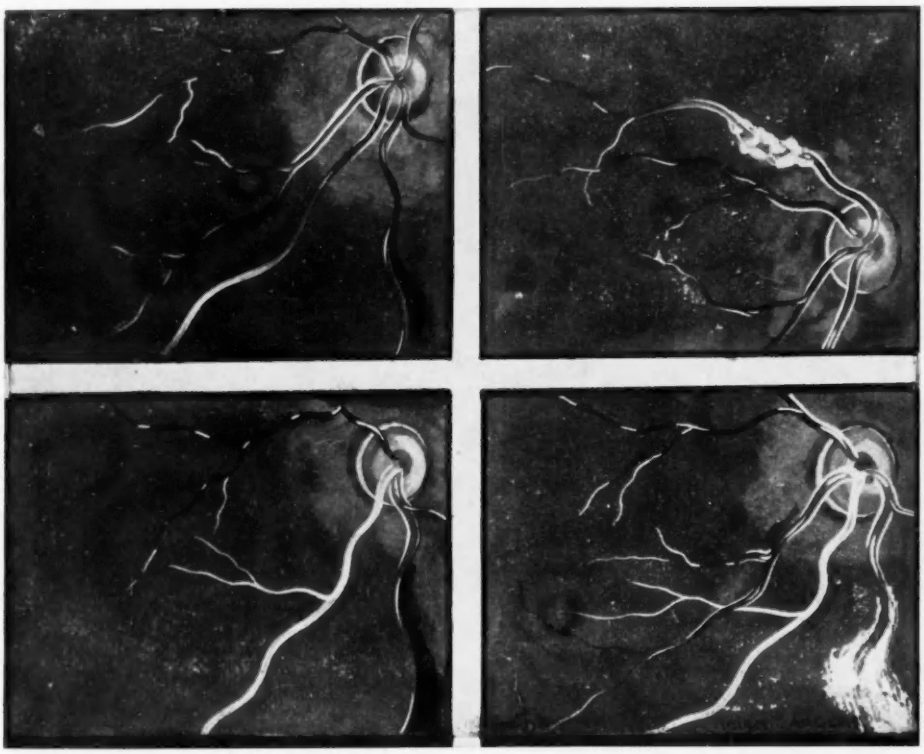


FIG. 2 — The earliest fundus pathology seen.

FIG. 3 — Recurrent hemorrhages. The ensheathment of the inferior temporal vein is now almost complete.

FIG. 4 — A further stage of perivasculitis development.

FIG. 5 — Contrasting the arterial perivasculitis and the venous ensheathment.

deep in the macular region a peculiar greyish, lace-like structure which involved almost the entire macular region and extended slightly upward tomporally in the shape of a pear, tipped, with the apex upward.

The fundus of the left eye was normal. There was some engorgement of the veins, and there seemed to be an increase in fine tortuosity of the veins as (This same picture, however, has continued throughout the entire time that the patient has been under observation. Notes have been made repeatedly regarding the appearance of the retinal vessels in the left eye, and there has been no change during the entire period of observation).

The von Pirquet reaction was strongly positive. The patient was placed on tu-

berculin therapy, using TR. (new tuberculin), starting with the serial dilution number one, minims I. Following the second injection, minims II, the patient developed a fresh hyphen-like hemorrhage along the course of the inferior nasal veins. The tuberculin was continued, however, in carefully controlled doses, the condition of the retina and the patient's temperature being watched carefully. There was a slow, steady, progressive improvement. The pupil was kept constantly dilated with homatropine. The relucency of the beam in the anterior chamber continued unchanged. At times it seemed to recede and at other times it was more marked, but never was there any descemititis nor were there any hemorrhages in the anterior chamber. The ocular tension remained unchanged. On April 7, 1934, the visual acuity was 2/15, and the patient could read, somewhat eccentrically, letters 7 to 14 (Jaeger). By May 19, 1934, there was definite evidence that the perivasculitis was beginning to increase. At this time, a fresh hemorrhage appeared along the same inferior temporal vessel as seen in figure 3. This was somewhat more extensive than the first hemorrhage which we had observed. By this time the entire inferior nasal artery was silver-white and completely ensheathed, as seen in figure 3. Also, the intra-ocular tension began to increase. Homatropine was discontinued and pilocarpine was prescribed. The tension of 28, 32, 45, and 48 mm. Hg., respectively, at one week intervals, dropped to 32 and remained there. A hemorrhage appeared on the superior nasal vein similar to that along the inferior nasal vein. Both hemorrhages were dark and broke through into the vitreous. Both were followed over a period of six months by a quite different type of perivasculitis. Large clumps of silvery-white fibers formed about the vessels, as seen in figures 4 and 5. Fresh hemorrhages appeared constantly from time to time, always lying along a vessel, as shown in figure 5, and in each instance the absorption was followed by the deposition of pearly, shining periphlebitis. The entire vascular tree was involved in the two forms of perivasculitis, even to the smallest visible vessels.

The visual acuity failed rapidly. Figure 6 reveals the only remaining field of vision which could be obtained at this time. The nerve head was sharply cupped, pale, and infiltrated, and the perivasculitis involved the surface of the nerve head as well.

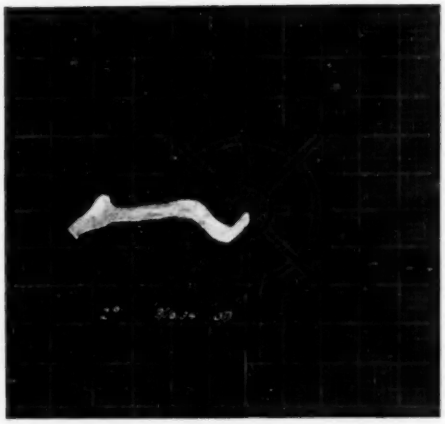


FIG. 6 — The last field of vision prior to complete blindness.

On August 12, 1934, the pupil was dilated with homatropine, and a developing retinal separation was discovered. This was limited to, and involved, practically the entire periphery. An interesting feature was that the separation, while relatively flat, still contained a large number of accordion-like concentric folds. It seemed as if the separation was occurring because of a radial contraction upon the retina by the blood vessels as a result of the very high degree of periphlebitis then established and becoming progressively more severe. The retinal separation continued to increase, and by January 1, 1936, it had advanced to the degree seen in figure 7. At this

FIG. 7 — The retinal separation in its final stage. The hole in the macula is drawn, perhaps, a bit smaller than actual size.

time, the eye became almost entirely blind. Shortly afterwards, complete blindness did occur, and soon a characteristic, small, punched-out hole in the macula developed, as shown on the composite drawing illustrating the final degree of retinal separation which occurred.

From this time to May 13, 1939, the eye was relatively quiet and painless. The tension continued between 32 mm. Hg., at the least, and 65 mm. Hg., at the most. Occasionally, the patient stated, he had some light perception in the right eye, and once or twice during this time he was able to trace out at arm's length the black and white contrast of the 6/45 Snellen letter.

On May 24, 1939, he complained for the first time of sensitivity to light in both eyes, which was associated with lacrimation. Three days following this, he reported to the office, and examination revealed a fine filamentous hyphemia adherent to the iris stroma, projecting into the anterior chamber, and reflected from the angle of the anterior chamber on to the posterior surface of the cornea. It seemed as if the entire hyphemia was supported by a net of fibrin. Two days later, a dome-shaped hyphemia appeared through the pupillary aperture from the posterior chamber. The margins of the dome were sharply outlined. Photophobia increased decidedly, and the tension mounted to 70 mm. Hg. This hemorrhage, almost a terminal condition considering the pathology, increased constantly and to a very marked degree.

Enucleation was recommended and was performed under avertin anesthesia July 10, 1939, with an implantation of a carbonized bone ball into Tenon's capsule.

Postoperative convalescence was uneventful. Before the patient was dis-

charged from the hospital, the photophobia which had been present (in the left eye) had disappeared entirely. The patient has returned to work. Since the operation, he has been seen from time to time, and, as stated previously, there have been no further changes whatsoever in the appearance of the retinal vessels of the left eye.

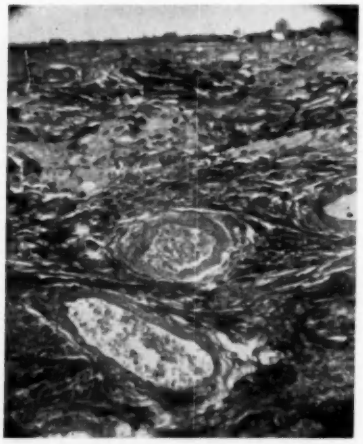


FIG. 8 — The high degree of choroidal sclerosis, the new formed connective tissue about the vessels.

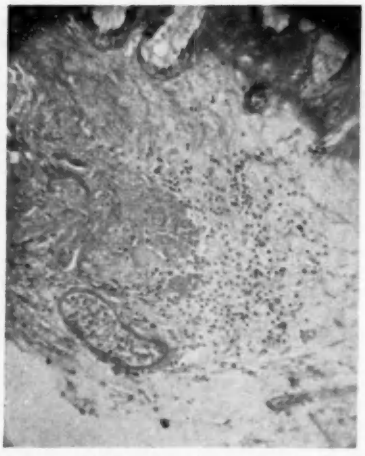


FIG. 9 — Retinal pathology, as seen close to the ora. The amount of connective tissue lying in the proximity of the vein shown is quite evident.

Microscopically, the various pathological changes are seen in figures 8 to 10, inclusive. The gross appearance of the globe, when sectioned anteroposteriorly, showed hyphemia and vitreous hemorrhages. Serial sections permitted detailed study. There was but little pathologic change in the corneal structure except for a pannus at the limbus, which could be explained on the basis of chronic irritation. The anterior chamber was shallow and was partially filled with hemorrhage and serum. The filtration angles were entirely obliterated by an anterior synechia (glaucoma).

The surface of the iris was covered by a new-formed fibrous tissue, the product of an organizing exudate. The stroma was atrophic, with much disturbance of its pigment content. Also, some new fibroblasts were replacing the iris stroma. All the blood vessels were sclerotic, and there was definite thickening of their walls. There was some atrophy of the pigment layer. The ciliary processes and body were atrophied, and there was evidence of some fibrous tissue proliferation.

FIG. 10 — New formed thickened blood vessels in the iris stroma.

The lens was normal. The choroid was sclerotic throughout, and some of the vessels were markedly engorged with blood. In one area there was a subchor-

oidal hemorrhage. The few remaining vessel walls show a thickening of their tissue (sclerosis).

There was evidence of chronic change throughout the retina, with some proliferation of the supporting tissue and atrophy of the neurological structure. There were many new, thickened blood vessels, in which definite perivasculitis was present. There was an occasional extravasation of blood into the altered retinal structure. There was separation of the retina in many different regions, largely at the periphery, with subretinal exudates.

There was a deep glaucomatous excavation at the nerve head. However, the nerve head itself revealed no definite pathology.

CONCLUSIONS

It is extremely difficult to make a definite pathological diagnosis of Eales' disease from the above pathology, but with the history and clinical findings, together with the general sclerosis of the blood vessels, much perivasculitis, areas of hemorrhage, a chronic process, and secondary glaucoma, all in a young individual, Eales' disease would be indicated. It is especially significant when one considers the ravages of vascular pathology in the diseased eye as compared with the almost normal to barely minimal pathological ophthalmoscopic appearance of the vessels in the opposite eye. From the standpoint of differential diagnosis, this case cannot be considered a simple instance of retinitis proliferans. The clinical course, the fundus pathology (in life), and the microscopic findings seem to suggest a state of high degree of generalized vascular disease separate from that possibility.

DISCUSSION

W. R. BUFFINGTON, M.D., New Orleans: Recurrent retinal and vitreous hemorrhage, or Eales' disease, is so rare that the opportunity to study a case clinically, to observe the progressing vascular changes over a period of years, and, finally, to make a complete histopathological study of the same is a real contribution. In most instances when such an eye becomes available for study it is impossible to determine what the initial pathologic process was because the obliterated retinal vessels are the same as those in thrombosis of the central vein. On the other hand, von Hippel in a study of a series of cases found that some of the obliterated veins still contained endothelial, epithelioid, and giant cells with perivascular nodules—all suggesting a tuberculous perivasculitis. In some cases definite tuberculous lesions were found in other parts of the eyes examined, thus giving strong confirmatory evidence that the symptoms complex of Eales' disease is a result of tuberculous periphlebitis. Wall and Kipp each reported two cases of recurrent vitreous hemorrhage in active pulmonary tuberculosis. Tuberculosis was present in 3 out of 5 of Finnoff's cases. Safar regards the disease as a primary periphlebitis affecting usually the smaller veins. Histologically, it resembles tuberculous phlebitis. Suffice it to say, the disease affects young people mostly. It is characterized by primary changes in the retinal blood vessels leading to recurrent hemorrhages.

In Jackson's review of this important subject, he states that blood dyscrasia and endocrine dysfunction are worthy at least of consideration, but if the hemorrhages are the result of a localized pathological weakening of the blood vessels, is it not a basic local vascular disease closely related to what one sees in cases due to tuberculosis? Eales' disease usually occurs in patients from 14 to 20 years of age. The symptoms are: slow pulse; dyspepsia; low spirits; lassitude. These all should be kept in mind. Finally, Jackson suggests, "It may well be that tuberculosis is not the essential cause of recurring hemorrhage into the vitreous, but some condition arising in tuberculous patients is the cause."

To summarize:

1. Recurrent intra-ocular hemorrhage is not a specific disease.
2. Tuberculosis of the retinal veins is a common cause.
3. Peripheral retinal veins are mostly affected.
4. Focal infection may be a probable cause.
5. Blood dyscrasia and gastro-intestinal diseases I think can be eliminated as direct causes.

In most of the cases reported, only peripheral vessels are affected. It might be said that massive vitreous hemorrhage is seen

only when the peripheral vessels are affected. It rarely if ever occurs when only the central vessels are diseased. The reason for this is anatomical and not pathological. In an active case, the report of which follows later, the picture shows the involvement of larger vessels encased in a perivascular fibrosis. When the media cleared up, it was found that peripheral retinal hemorrhages, temporally and below, indicated that vitreous hemorrhage came from these vessels and not from the larger ones involved. We may assume that in tuberculosis of the retinal blood vessels either the central or peripheral vessels may be affected or both may be affected at the same time in the same eye.

Eales' disease results from a phlebitis or periphlebitis due to a tuberculous blood stream infection. In all forms of tuberculosis of the retinal blood vessels the retinal veins are more frequently attacked. The questions arise: "Why the predilection for the veins? Are the veins more vulnerable, or does the venous blood offer less resistance to the invading germ or its toxin?"

The anatomical changes in retinal vascular tuberculosis follow as a rule in regular order. There are (1) endophlebitis, and (2) periphlebitis. These manifestations are followed by a tuberculous invasion of the adjacent tissues. The veins become thrombotic; later, necrotic; and then the hemorrhages occur which are so often seen near the vessels. Because of thrombotic phlebitis, the veins become engorged, enlarged, and tortuous.

CASE REPORT

Mrs. B., aged 29 years, suffered loss of vision in the left eye in July, 1938. The vision in her right eye was 20/20, and that in the left, poor light perception. Ocular examination revealed an absence of the fundus reflex which was proved to be due to a massive vitreous hemorrhage. Careful physical and laboratory examinations revealed normal findings except for an antral infection. A Caldwell-Luc operation was done. In a short time the vitreous was clear of blood. The vision in the left eye became 20/20, or normal. Doctor Martin stated that after the vitreous had cleared, chorioretinal changes were seen in the temporal periphery of the fundus. Intradermal old tuberculin test, 1 to 100,000, gave a mildly positive reaction. Intradermal old tuberculin test, 1 to 10,000, gave a strongly positive reaction. In March, 1939, there were no active symptoms. The vision was still normal. On August 29, 1940, the patient returned with symptoms similar to those present in July, right eye normal; left, vision reduced to light perception due to a massive vitreous hemorrhage. The vitreous hemorrhage was rapidly absorbed so that by September 20, 1940, the vision in the right eye had increased from light perception to 20/30.

In addition to the atrophic lesion seen by Doctor Martin following clearing of the vitreous in 1938, examination with the ophthalmoscope revealed extensive, diffuse retinal hemorrhages in the peripheral fundus, temporally and below. Unquestionably, the massive vitreous hemorrhage came from this area. In addition, the central fundus changes which occurred between the first and second attacks were:

1. Perivascular fibrosis along the temporal veins.

2. A tubercle on the upper temporal vein at the disc margin.

3. A striking change in the caliber of the temporal vessels from disc to periphery.

In the course of Eales' disease, examination with the ophthalmolscope will reveal the following:

1. (Slide). Early stage: Grey-white patches on or near the vessels.

2. (Slide). Later stage: Veins distorted, irregular in caliber, and in places entirely occluded.

3. (Slide). More advanced stage: Distinct perivascular sheathing occurs as in all forms of periphlebitis.

4. (Slide). Still more advanced stage: Probably a reparative process; newly formed blood vessels are seen.

EDMUND B. SPAETH, M.D., Philadelphia: There is just one thing further I want to add, which apparently I did not emphasize, and that is the fact that the fundus and vessels in the other eye were absolutely normal, and clinically the major portion of the pathology was confined to the veins. It was only later that the arterial pathology appeared, and that appeared as the perivasculitis of a high degree, where the white fibers threaded out from it. Perivasculitis and periphlebitis continued as the similar white streaks that Doctor Buffington showed in his case here.

THE FUNDI IN HYPERTENSIVE DISEASE AND AFTER SPLANCHNICECTOMY

F. Bruce Fralick, M.D.
and
Max M. Peet, M.D.
BY INVITATION
ANN ARBOR, MICHIGAN

Withdrawn from publication by request.

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

THE MANAGEMENT OF SINUSITIS IN CASES OF BRONCHIECTASIS

ROBERT L. GOODALE, M.D.
BOSTON

SINUSITIS is a frequent complication of bronchiectasis, as we all know. It's prevalence varies according to the experiences of different observers, but I think all agree that its occurrence is sufficiently frequent to constitute an essential part of the picture of bronchiectasis. My purpose in presenting this paper is to report some observations regarding the surgical management of such cases as are suitable for operation and outline briefly the points to be considered in cases where operation is inadvisable.

Recently I had an opportunity to survey 150 cases of bronchiectasis at the pulmonary clinic of the Massachusetts General Hospital and to evaluate the effect of sinus surgery both on the symptomatology and the economic effectiveness of the patients. The following observations are drawn from this study. Over 90 per cent had some degree of sinusitis. The patients were classified according to: (1) the severity of this complication, (2) their age, (3) susceptibility to infection of the upper respiratory tract, (4) the extent of the pulmonary process, and (5) their ability to withstand operative procedures. All these considerations make it necessary to individualize each case. This means not only that consultations and close cooperation are necessary with the general medical service, the thoracic surgeon, and the bronchoscopic service, but also within the field of rhinology those measures should be applied which are particularly indicated for the individual patient.

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

The local problem regarding the nose and sinuses remains for the most part the same as in uncomplicated cases, and here I follow the principles described by Porter[3] in the treatment of acute and chronic sinusitis. The pulmonary element adds to this picture the factors of re-infection of the chest from above and of the additional load of infection which the patient must bear. In general, the aim of any treatment of the sinuses in these cases is the drainage of infected secretions, the removal of diseased tissue, or the correction of factors which cause such tissue to be infected. Of course, it is not possible to remove the bronchiectatic cavity by sinus surgery. It can be relieved, however, of whatever infection may reach it from the sinuses by any of the routes described by Fenton and Larsell.[2] The removal of one focus of infection can lighten the total load so that the patient will have more strength to combat the thoracic disease.

In the series of cases which I have studied,[1] I found that one-third of the patients had developed bronchiectasis before the age of 10. This group presents some factors which set it apart from the group consisting of older patients. Bronchiectasis in the younger patients is attributed to essentially pulmonary diseases rather than to sinusitis. They give a definite history of pneumonia, pleurisy, whooping cough, or bronchitis as the direct precursor of their disease. However, these patients seem to be extremely susceptible to colds and in many cases have developed sinusitis either at the time of the original infection or afterwards. They have low re-

sistance to all infections. As they do not tolerate surgery as well as children without bronchiectasis, extensive sinus surgery has not been indicated.

In this group of younger patients the nasal problem seems to be rather mechanical in nature. The patients do not seem to be able to keep the nasal passages free and clear from secretion. Their turbinates are swollen and often are bathed in tenacious mucopus, which is endured without an attempt being made to get rid of it. Some of the children, in fact, do not know how to blow their nose, and for many, even forceful blowing does not bring relief. With this retention of pus the patient is headed for more chronic infection of the sinuses.

When indicated, surgical procedures should aim at drainage in treating children with this condition. Intranasal window operations on the antrum, removal of anterior tips of the middle turbinates, and adenoidectomy are the operations usually performed. Postoperatively, suction or lavage of the antra helps to remove what secretion the patient cannot blow out. In cases where operation is contraindicated, I have used suction. In some cases the benefit from this type of treatment is marked, and in most of the others, even where the objective improvement is only partial, there is subjective relief which lasts from three to four days. In any event this treatment seems to be a valuable adjunct to other procedures employed in the management of sinusitis.

Finally, in this group of patients who are below the age of 10, strict attention should be paid to general hygiene. As a rule, a pediatrician is requested to take care of such details as diet, nursing management (either in the home, sanitarium, or hospital), and immunization with bacterial vaccines. He also should carefully take into consideration the environmental factors and, where it is possible, should consider a change to a better climate for patients whom he believes will be benefited by such a change.

There is another group of patients who must be treated conservatively. This consists of patients who have endured their bronchiectasis and sinusitis well past middle age. For many of them the expectancy for many more years of life is slight. Palliative treatment or minor surgical procedures will give the best results.

In patients of the third age group, consisting of young adults and adolescents who are able to tolerate surgery sufficiently well, radical procedures can be considered. Unfortunately, in this group there are some patients who have such an overwhelming amount of disease that conservative measures are all that can be attempted. But for those people who can tolerate surgery, a radical procedure offers the greatest amount of relief. Some may not need more than correction of those factors which contribute to re-infection of the sinuses. They may not have an actual chronic disease, but nevertheless they are subject to repeated attacks of acute sinusitis. Here again, submucous resection, removal of middle turbinates, intranasal antrum operations, and tonsillectomy may be the only surgery required.

The very high incidence of severe chronic sinusitis in this age group is remarkable. Frequently, x-ray examination shows not only marked thickening and retained secretion, but also bone reaction. These severe cases may be of the quiescent type, and the patient's symptoms may not coincide with the amount of disease that exists. In fact, at times intranasal examination will fail to indicate how really severe is the infection. For this reason, x-ray examination of the sinuses is absolutely essential, and in many cases more than one series of films may be necessary to evaluate the severity of the disease.

I have been impressed by the number of patients who suffer from pansinusitis. In fact, the ethmoids seem to be infected as frequently as the antra, and the combination of antral and ethmoidal infection is common. Also, the sphenoidal sinuses seem more often to be infected than was previously considered to be the case. I am inclined to give the ethmoids greater and greater consideration, as I see the results of adequate and inadequate sinus surgery. I have not observed the dryness and crust formation which many otolaryngologists fear may result from complete ethmoidectomy. In my opinion, purulent crusts are more apt to occur when some infected cavity remains. The best results have been in those cases where the operation has been thorough and where the recuperative powers of the patient were good to begin with.

I will not go into the technics of operation except to say that for radical surgery on the antrum, I favor a canine fossa approach, and for the ethmoid and sphenoid, a combination of intranasal and transantral route. An external orbital approach in some cases may be the one of choice, especially where the frontal sinus is involved.

In general, the points to be considered in selecting a case for radical operation are the same as those to be considered in cases which do not have a chest complication; but as I have said previously, the chest complication adds new factors, namely, the dangers of re-infection of the chest from above and whether the patient is able to withstand concurrently both the insult of multiple infections and operative procedures. Some patients have such a degree of general infirmity that they do not tolerate much surgery at one time. As I have pointed out, the age of the patient also is to be considered.

In addition, there is a seasonal factor which applies especially to us in New England. The danger of epidemic infections during the fall, winter, and early spring is very real for patients suffering from pulmonary disease. They are extremely susceptible to repeated attacks of pneumonia. Minor operations, not to mention major ones, frequently will precipitate fatal results. For this reason the thoracic service at the Massachusetts General Hospital has decided that lobectomies should be performed preferably during the late spring and summer months, and I feel that it is a good example to follow in operating on the sinuses of patients with pulmonary involvement. Then, too, when the postoperative period occurs during the summer months, there is a long interval during which the patient is free from infection, and healthy repair of the operative field is facilitated. I wish to emphasize, especially, the undesirability of operating upon the sinuses whenever there is an epidemic of head colds. Also, there should not be any remnant of acute infection latent in the sinuses at the time of the operation. The pulmonary infection should be as quiescent as possible. Postural drainage is advocated routinely for bronchiectatic patients who undergo sinus surgery at the pulmonary clinic of the Massachusetts General Hospital. It is advisable that the secretions from the lungs drain as completely as possible in this manner previous to the surgical procedure for sinusitis inasmuch as it is necessary that the patient remain quiet for one or two days following surgery. In one or two instances, postural drainage following surgery has stimulated postoperative bleeding. On the whole, sedatives which reduce cough should not be used, as their effect on the patient tends to allow secretions to accumulate in the chest. If the patient is in a ward, he should be isolated whenever an acute infection develops among the other patients.

With regard to the operation, I have already mentioned that it is desirable to

do as complete an operation as the general condition of the patient will allow. If possible, the operation should be completed in one stage. When much has to be done, or when the patient's general condition makes it necessary, the operative procedure should be divided into several stages. It is better not to do too much surgery at any one time. For instance, at the time of the first operation, it may be possible only to correct a badly deviated septum. At the time of the second operation, only the antrum or ethmoid on one side can be drained, leaving the opposite side for still a third procedure. In such a situation, I think it is best not to perform the operations at short intervals. The patient should be given enough time between procedures to recover from whatever degree of postoperative reaction he has experienced.

One other point which is extremely important is to make adequate bacteriological studies preoperatively. This should also be done of the pus obtained at the time of operation in order that any necessity for chemotherapy can be anticipated.

In regard to anesthesia, I have always preferred a local anesthetic. By using ether, there is the danger of lighting up the pulmonary infection. Recently, the medical service and the thoracic surgeons at the pulmonary clinic of the Massachusetts General Hospital have seen no contraindications to the use of ether. In fact, lobectomy itself is done frequently under general anesthesia.

I should like to bring out one other point — the infection in the sinuses and the infection in the chest can be considered as two separate foci, which together constitute the patient's disability. The removal of one without the removal of the other is an incomplete operative procedure. Just as complete sinus surgery is better than an incomplete procedure, the best results follow when lobectomy plus a thorough sinus operation are performed.

Finally, the only way to insure success from operation is to keep the patient under observation and treat subsequent conditions which threaten a return of sinusitis, such as recurrent infections of the upper respiratory tract. This follow-up and after-care are as much a part of the management program as the preoperative consideration of the case and the operation itself.

REFERENCES

1. Goodale, R. L.: An analysis of 75 cases of bronchiectasis from the viewpoint of sinus infection, Ann. Otol., Rhin. and Laryng. 47:347-359 (Sept.) 1938.
2. Larsell, O., and Fenton, R. A.: Lymphatic pathways from the nose, Arch. Otolaryng. 24:696-713 (Dec.) 1936.
3. Porter, C. T.: Sinusitis: The present rationale of treatment. Ann. Otol., Rhin. and Laryng. 48:769 (Sept.) 1939.

DISCUSSION

C. T. Porter, M.D., Boston: I want to compliment Doctor Goodale on his excellent paper. I do not believe that many of us realize how many hours of hard work have been necessary in accumulating all the data which it contains. The job has been difficult, and Doctor Goodale has called attention to a feature in medicine closely related to our own specialty, which is perhaps not as broadly appreciated as it should be. A great many patients with this type of disease go from one physician to another and from one hospital to another without receiving adequate treatment, because the teamwork between physicians at various pulmonary and thoracic clinics of the larger institutions is not fully sufficient. When I first began making rounds at the pulmonary clinics, I was amazed at the number of patients with bronchiectasis who came for diagnosis and treatment.

I wish Doctor Goodale had had time, or had deemed it properly significant, to say something about the incipient cause of the so-called repeated cold which leads to exacerbation of bronchiectasis. His paper deals with the disease as it already exists. I wish he had been able to include the fact that very frequently chronic bronchiectatic exacerbations and colds, particularly in children, are

in reality sinus conditions which precede or antedate the bronchiectatic condition. In adults and older children, it does occur more often after an attack of pneumonia, but in younger children, it frequently occurs after repeated attacks of bronchitis, secondary to infection of the ethmoidal sinuses. I am sure that Doctor Goodale has something to say regarding this, and we would be very much obliged to him for any remarks he may add in closing.

I agree with his method of operative procedure. A local anesthetic is my choice. Any sinus operation can be performed, with comfort to the patient, under a local anesthetic supplemented by some form of barbiturate.

I wish Doctor Goodale would discuss further the conservative local treatment, particularly in cases of children. He did not stress that quite enough. This is extremely important, and the results are gratifying.

HENRY M. GOODYEAR, M.D., Cincinnati: Nasal sinus infection in the presence of a well established bronchiectasis should receive special consideration due to their close relation. Not infrequently I have seen a severe bronchial cough greatly relieved within twenty-four to thirty-six hours after a single injection of iodized oil into an acutely infected antrum.

Infection of the antra and ethmoidal cells are frequently associated with bronchiectasis, as Doctor Goodale has emphasized, and the antra are to be considered first in any case of infection of the ethmoidal sinuses. A chronic antral disease never occurs without some infection of its adjacent ethmoidal cells. Thus, to attack an antral infection is the first step in the treatment of any accompanying infection of the ethmoidal sinuses.

Of course, more important than treament of bronchiectasis is that of prophylaxis. Doctor Goodale, in his careful study, states that one-third of his patients developed bronchiectasis before the age of 10. I believe that at this early age the child is too frequently treated for a chronic bronchial cough without due regard for an underlying antral and ethmoidal infection. Let the chin be raised high against the x-ray plate and the antra will be revealed on the film even in the case of a child. Here, roentgenograms of the antra after iodized oil has been injected into them will definitely indicate infection, if present, and, at the same time the oil offers an important adjunct in treatment.

It is often surprising to find how easily a small double curved cannula will pass into the antrum through the middle meatus of a child. If the cannula must be passed through the inferior meatus, I have found that a straight needle is most helpful and causes no pain when the following precautions are taken: Cocainize the area with a very small applicator and press the needle slowly, with a slight rotating motion and without pressure on either the turbinate or the nasal septum. When this method is used, the child will not complain.

Injections consisting of a 27 per cent solution of iodized oil into the antra should be made at intervals of ten days to two weeks or longer, as improvement is indicated by periodic roentgenographs. I have long since abandoned treatment by irrigations in cases of subacute and chronic antral infections.

Should treatment consisting of injections of oil fail, an opening of generous proportions should be made under the inferior turbinate. Recently, I saw in consultation a medical student, aged 24, upon whom I had made bilateral intranasal antral openings for chronic infection when he was 10 years of age. The openings, unbeknown to the student, were still patent after fourteen years, and he had been free of any nasal trouble.

I rarely operate upon the ethmoidal cells of a child because in doing so the middle turbinate may be broken medially and occasionally the floor is cut from a large bullae cell. Usually, in children, if the infected antrum is adequately treated, the infection in the ethmoidal cells will clear up.

Doctor Goodale mentioned whooping cough, and I am sure that this disease is not given sufficient emphasis as a forerunner of bronchiectasis. If the cough is not subsiding normally within six weeks, sunshine and a warm climate should be sought until the child has recovered, or he should be kept indoors where he is protected from wet, cold, and changeable weather.

I cannot stress too strongly our responsibility in treating children who have a definite ethmoidal and antral infection and a cough following a cold. No effort should be too great to get these children well before a bronchiectasis develops, which, as you know, can never be cured and is to be dreaded even more than tuberculosis.

ROBERT L. GOODALE, M.D., Boston: Thank you very much for your criticisms and suggestions.

In reply to Doctor Porter, the difficulty I have found in blaming some preceding disease for the bronchiectasis has been due to the fact that most of the patients whom I have seen have had bronchiectasis for a con-

siderable length of time and have forgotten all the features that surrounded the onset. I have been very hesitant in blaming the sinuses, and perhaps have leaned over backwards in an effort to avoid doing so. These patients have attributed essentially pulmonary conditions or whooping cough as the disease which preceded the bronchiectasis. At the time of the pulmonary disease, or subsequently, they developed a marked degree of sinusitis due to repeated infections of the upper part of the respiratory tract. It is perfectly true that after bronchiectasis has been established, subsequent attacks of sinusitis aggravate the bronchiectasis.

Conservative treatment is essential for children, and much information is yet to be gained with regard to this phase. I mention conservative surgery and general hygiene which, of course, could be elaborated indefinately. I believe that each case must be treated individually, and that is what I have tried to stress. All physicians concerned in the treatment of a patient with this disease should cooperate closely.

Treatment of infected antra is fully as important as that of ethmoidal sinuses. When I stressed the necessity for treatment of the ethmoidal sinuses, I did not mean to omit infections of the antra. In the case of a child, if conservative medical treatment is inadequate, the antrum should be opened and drained.

I have not used iodized oil in treating infections of the antra. I use a normal saline solution. I have tried displacement along with the suction, but did not mention this in my paper. It has helped a great deal in clearing out secretions from the antra and ethmoidal sinuses. However, my experience with this type of treatment has not been extensive enough to report.

In this series, the patients did not attribute their bronchiectasis to whooping cough, although I suspect that a great many had had whooping cough.

I received a letter from Doctor R. A. Fenton, who was unable to be present to discuss my paper, and I would like to read a part of it. He says, "May I suggest that the effect of bronchial swelling about the lymphnoids, infected by the pulmonary blood stream, seems a not inferquent cause of bronchiectasis."

ACUTE LARYNGOTRACHEOBRONCHITIS

Analysis of Sixty-Two Cases with Reports of Autopsies of Eight Cases

HENRY BOYLAN ORTON, M.D., ELLIS L. SMITH, M.D.,
BY INVITATION
HORACE O. BELL, M.D., AND RALPH A. FORD, M.D.
BY INVITATION BY INVITATION
NEWARK, NEW JERSEY

INTRODUCTION

ACUTE laryngotracheobronchitis is an infection of the respiratory tract, occurring most frequently in children under two years of age. It is characterized usually by a primary inflammation of the pharynx, with later involvement of the larynx and trachea, extending to the bronchi, and is accompanied by a sticky, gummy exudate, which produces variable respiratory obstruction with severe symptoms of toxicity. The etiology has not been definitely determined, but many organisms obtained from laryngeal and tracheal cultures have been incriminated. Recently, virus has been suggested as the primary invader preparing the way for secondary bacterial invasion, especially by the hemolytic streptococcus.

Greenwood[12] states that it is "an inflammatory disease of the laryngeal intima, usually secondary to an acute upper respiratory infection, and generally associated with pathological changes in the lower respiratory tract." Jackson divides acute inflammations of the larynx, essentially, into (a) specific acute laryngitis, and (b) nonspecific acute laryngitis. He states, "Acute specific laryngitis is an infective disease with a definite course and a self-limited termination. Acute nonspecific laryngitis is due to causes other than infection and does not follow a regular course."

We agree with Evans[8] when he speaks of acute laryngotracheobronchitis as a disease of paramount importance to be recognized by otorhinolaryngologists, pediatricians, and general practitioners. The fact that the most expert efforts often fail to change the fatal trend of this malady has served in the past to make some of us despair of attempting to do anything. It is, therefore, extremely important that any measure which seems promising should be given a thorough trial, even though its mode of action is not entirely clear. The problems pertaining to treatment have been discussed by many. The mortality rate still is high, but without the present type of adequate facilities and competent nursing it would be higher.[5]

Acute laryngotracheobronchitis is by no means a new clinical entity. However, the marked increase in its incidence in our section of the country during the fall and winter of 1939-1940 again has brought it to our attention.

The purpose of this paper is to define terms, giving the corresponding clinical picture; show the different stages and factors as the process develops involving the various anatomical areas, the differential diagnosis, and treatment, together with reports of eight autopsies; and finally to report a survey of 62 cases of acute laryngotracheobronchitis seen and

Presented at the Forty-Fifth Annual Session of the American Academy of Ophthalmology and Otolaryngology, October 6 to 10, 1940, Cleveland, Ohio.

From the Department of Rhinolaryngology and Bronchology, Essex County Isolation Hospital, Belleville, New Jersey.

treated at the Essex County Isolation Hospital during the past four years, or from 1936 to 1940. An effort is made to evaluate the various methods of treatment, both medical and surgical. We have made a special effort to try to judge or evaluate the results obtained by intubation, tracheotomy, and moist cool air. This phase is described in detail under "treatment."

We compare our results with the statistics of other authors. (See Table I.)

This series of cases comprises both mild and severe types of laryngotracheobronchitis. In the mild form, when the patient is given prompt and effective treatment, the disease may never reach the severe stage which necessitates surgical intervention.

We agree with Brennemann[3] in the following statement:

> A sharp differentiation, according to the precise nature of the involvement in a given case, is not always a simple matter, especially as one must find an exact place in a series of manifestations that extend in severity all the way from simple catarrhal laryngitis to a rapidly fatal fulminating trachitis.

We do not only classify those patients who required tracheotomy, intubation, or bronchoscopic aspiration and those who died, but we also include cases in which a clinical diagnosis of laryngotracheobronchitis was made and where a surgical procedure was not necessary.

HISTORICAL DATA

MacCready[15] gives a very detailed report with a complete bibliography concerning the history of acute laryngotracheobronchitis. In 1928, Baum[2] in reporting a series of 24 cases brought out that in his experience intubation gave better results than tracheotomy. In a series of 38 cases, Gittins,[11] in 1936, pointed out that the mechanical obstruction was more serious than the type of infection. In 1933, Richards[17] made the first extensive pathological study of the condition. This was followed, in 1938,[18] by another interesting article in which he presented the possible use of sulfanilamide.

In 1939, Evans[8] reported a few cases in which he used a bacteriophage to liquify the broncheal secretions, which apparently was successful. In 1939, Galloway[10] reported 10 cases in which he advocated postural drainage to assist the patient in expelling the secretion from the broncheal tree. In 1940, Felts[9] in his series of 19 cases advocated the use of a room supersaturated with moisture. During the fall of 1939 and the winter of 1940, we treated patients with this condition by placing them in a room supersaturated with moisture in which the temperature was 70 degrees F. at all times, plus additional moisture in an oxygen tent, and the results were very gratifying. Davison,[7] however, must be given the credit for first bringing this type of treatment to the attention of the medical profession. He described it in a paper entitled, "Some Observations on the Control of Temperature and Humidity in Oxygen Tents," which was read before the meeting of the Eastern Section of the American Laryngological, Rhinological and Otological Society, held in Pittsburgh in January, 1940.

In all, over 300 cases, severe enough to require hospitalization, have been reported since 1918.

ANALYSIS OF CASES

The 62 cases of acute laryngotracheobronchitis, which we are reporting, were treated at the Essex County Isolation Hospital. Over one-half of the patients gave a history of previous cold or infection of the upper part of the respiratory tract, and the predominating organism was streptococcus. In our series we have 40 males and 2 females. Forty-seven of these patients were under three years of age, and the ages of the others extended

over the first decade. There were forty-five cures and seventeen deaths. In the case of two deaths, the patients were in a moribund condition on admission.

We are of the opinion that intubation alone is certainly not the procedure of choice as shown by the following data:

Intubation alone was performed on 8 patients, and only 1 recovered.

Tracheotomy alone was performed on 4 patients, 2 of whom recovered, resulting in a mortality rate of 50 per cent.

It is interesting to note, however, that with a combination of intubation and tracheotomy, which was done in 16 cases, 11 patients recovered, or 68 per cent recovered and 32 per cent died.

When intubation and tracheotomy both are carried out, we feel that intubation tides the patient over until tracheotomy can be done. Intubation is a deciding factor in bringing about a reaction from respiratory shock in these dyspneic patients, with the exception that in a case of acute laryngotracheobronchitis, which is accompanied by supraglottic swelling, tracheotomy must be done at once.

In 29 of our cases where some mechanical means was used for relief of dyspnea, 26 were children under three years of age. During the past year, 16 children were tracheotomized, 5 of whom died, giving a mortality rate of 31.25 per cent for this series. It is our belief that tracheotomy is the operation of choice and should be done as soon as possible.

Sulfanilamide was given to 20 patients, 13 of whom recovered, sulfapyridine was given to 3 patients, 2 of whom recovered, and there were 15 patients to whom both drugs were administered in addition to some surgical intervention, 7 of whom recovered. Sulfanilamide and sulfapyridine were administered to 8 patients in whom intervention by mechanical means was not carried out, and all of them recovered.

In the Essex County Isolation Hospital sulfanilamide is given routinely to all patients who are suspected of having acute laryngotracheobronchitis until the report on the laryngeal culture has been made, after which treatment is instituted accordingly. It is quite possible that many of the patients to whom these drugs were given had a mild form of the disease.

For comparison, out of 38 patients to whom neither drug was administered, 29 recovered, and of those recovered, streptococcus was found to be the predominating organism.

We believe that although sulfanilamide and sulfapyridine are not specific in this disease, they do seem to have some value.

We treated 15 patients by placing them in a room supersaturated with moisture and in which the temperature was 70 degrees F. Ten of them recovered. We are of the opinion that this form of treatment is a deciding factor in lowering the mortality rate of this disease.

TABLE I

Name	*Cases*	*Gross Mortality*	*Tracheotomies*	*Deaths*	*Tracheotomy Mortality*	*Dates*
Gittins[11]	32	39 %	20	12	60 %	1936
Smith[20]	43	9.3	12	4	33	1936
Baum[2]	24	41	17	9	53	1928
Richards[17]	28	40	23	12	50	1937
Felts[9]	19	21	17	4	23	1940
Orton	62	28	20	7	35	1940
Galloway[10]	10	20	10	2	20	1939
Davison[7]	17	11.7	9	1	11.1	1940
Brennemann[3]	45	42.2	9	1	11.1	1938

ETIOLOGY

Acute laryngotracheobronchitis is an inflammation of the mucous membrane of the larynx, trachea, and bronchi, usually preceded by symptoms consisting of infection of the upper part of the respiratory tract, usually rhinitis. In the absence of fever and a history of a preceding cold, the question as to the etiological factor is sometimes difficult, as brought out by Johnson.[14]

The cause, however, may be primary in the larynx or subglottic region. Occasionally it follows the aspiration of a foreign body of vegetable origin. The disease is more prevalent in infants and young children, although adults are not immune. This condition can, and does occur, in adults, as reported by Berry.[1] His case showed pure cultures of staphylococcus aureus hemolyticus with an abundant crusting suppurative infection of the entire respiratory tract. Direct examination of the smears taken from the larynx and trachea usually reveal a mixed infection of staphylococci, and pnuemococci. In some cases pure cultures will be found. The disease, as a rule, is far more severe in children under two years of age, probably due to the smallness of the subglottic area. The younger the child, apparently, the more severe is the infection. Out of our series of 62 cases, 47 were under three years of age. No specific organism has yet been proven as the causative agent of this disease. Most writers have found streptococcus to be the predominating organism. In forty-five laryngeal cultures, we found eleven with streptococcus, thirteen with streptococcus and staphylococcus, ten with streptococcus and pneumococcus, four with staphylococcus, two with pneumococcus, four with streptococcus, staphylococcus, and pneumococcus, and one with staphylococcus and pneumococcus.

FIG. 1 — Edema of the submucosal structures (A) of the trachea.

It has been suggested that a filterable virus may play a part in this disease and prepares the way for secondary invaders. However, this assumption has not been proven. The low blood count found in some of our patients suggests a virus disease.

PATHOLOGY

Clerf states,[6]

The gravest pathological finding is the marked subglottic swelling.

He further states,

This disease remains one of the most serious that has to be dealt with in children.

The disease depends on the existing causative organism. In all types of infection, especially during the early stages, there is an inflammatory reaction. Fifty-one patients in our series had gross pathologic changes in the larynx, epiglottis, cords, arytenoid, subglottic area, and trachea.

In the streptococcic type the infection is associated with marked fiery redness and swelling of the subglottic and tracheal regions, together with a pronounced velvety appearance of the tracheal mucosa. The true cords, however, may show comparatively little reaction. As the disease progresses, necrotic, gangrenous pseudomembranes may be seen extending down to the tracheal bifurcation and into the main bronchi. The subglottic swelling causes mild dyspnea early in the disease. Later, the obstructive, gangrenous pseudomembrane is responsible for more pronounced dyspnea, which is often extreme and leads to emergency surgical measures.

FIG. 2 — (A) Showing purulent exudate of the trachea, (B) adherent to the mucosa. Edema and infiltration with polymorphonuclear leukocytes of the underlying tissues.

If, however, the causative agent is staphylococcus, the inflammatory reaction of the tracheal and pharyngeal mucosa is practically always accompanied by thick, dirty-grey, tenacious mucous plugs which tend to dry and crust, and rapidly cause marked progressive obstructive symptoms. In our series there were 6 patients who had a pseudomembrane in the larynx. Frequently some of these crusts can be seen early in the infection, covering the vocal cords and obstructing the glottis. Removal of the tracheal and bronchial crusts does not reveal necrosis of the tracheal mucosa. This manifestation, however, is frequent in the later stages of the streptococcic type.

Bacteriologically, we found in our series the causative organisms as follows:

11 cases, streptococcus alone
13 cases, streptococcus and staphylococcus
10 cases, streptococcus and pneumococcus
4 cases, staphylococcus
2 cases, pneumococcus
4 cases, streptococcus, staphylococcus, pneumococcus
1 case, staphylococcus and pneumococcus

45 cases — Total

We have nothing startling to report in the blood picture, other than, due to the infection, there was a marked shift to the left, which was noted in the vast majority of the patients. However, late in our series, we attempted to ascertain the CO_2 content of the blood. This was done in only 6 cases, which is too small a number from which to make definite deductions. In 3 cases, where the CO_2 content was 41 or below, the patients died. The other 3 patients with a CO_2 content above 42 survived.

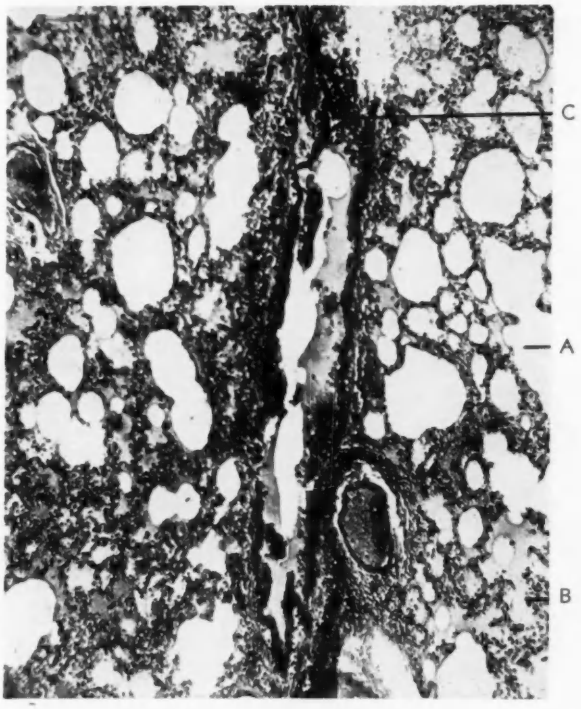


FIG. 3 — (A) Emphysema. (B) Atelectasis and interstitial pneumonitis. (C) Purulent exudate in terminal bronchus.

In this paper we report in detail the autopsies of 8 patients who died as a result of acute laryngotracheobronchitis. In summarizing these autopsies we find that the anterior nares revealed some crusting and mucopurulent material, emphasizing the existence of an infection of the upper part of the respiratory tract. The pharynx and tonsils were inflamed. The mucous membrane of the larynx, trachea, and large bronchi was swollen, hyperemic, and edematous. To nearly its entire extent, this mucous membrane contained a thick, somewhat adherent mucopurulent exudate which separated easily from the underlying tissues and then left no gross area of erosion.

The laryngoscopic examination often revealed a deep red, swollen subglottic mucosa, which was covered with yellowish crusts or a mucopurulent material. The swelling of the subglottic area was so great at times that very little air way remained, and this was further obstructed by the out-pouring of thick, tenacious secretion. Occasionally, extensive supraglottic edema also was present, especially of the epiglottis — a condition which may be easily detected by digital examination.

The bronchoscopic examination often revealed thick, tenacious secretion in the trachea which obstructed the openings of the bronchi. The tracheal mucosa was red and swollen, but with further progress of the disease, as Brennemann[3] states,

> The intensely red mucosa has been lost and is replaced throughout the tracheal tree by

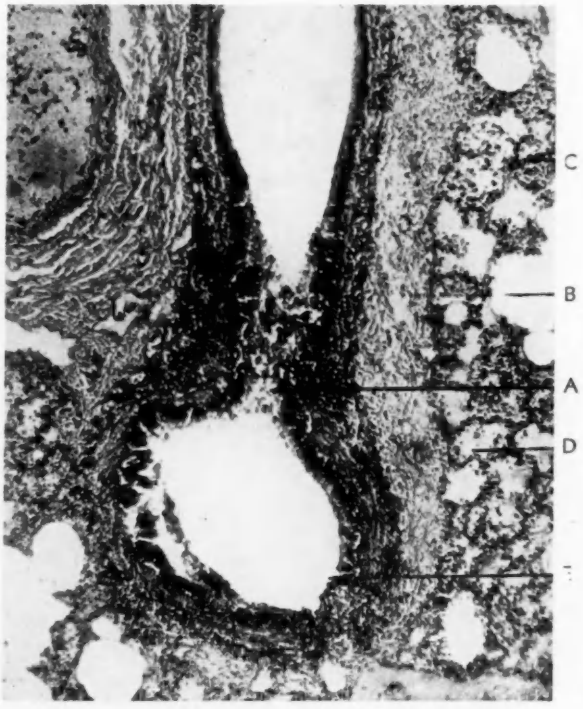


FIG. 4 — (A) Showing mucous plug in small bronchus containing in addition many cellular elements, (B) emphysema of alveolar spaces, (C) atelectasis and interstitial pneumonitis, (D) mucoid exudate in small alveoli, (E) ulceration and partial destruction of epithelial lining of bronchiole.

an exudate with a dry, glazed, grey surface. It is thick enough to cause a decided narrowing of the tracheal lumen, and in some instances to cause such a narrowing that even the smallest aspirator cannot be passed where previously a small bronchoscope had entered.

On cross-section we would find the parenchyma of the lung somewhat congested and containing small amounts of thin, sanguinous fluid, but there was no gross evidence of consolidation, and the lungs seemed to be well aerated. The smaller bronchioles were red and congested with a moderate amount of glary, bloody material. The glands at the hila and along the large bronchi and trachea were enlarged and somewhat congested. In other cases throughout the lobes of both lungs were scattered small areas of patchy consolidation where the surfaces appeared red and congested and the smaller ramifications of the bronchial tree contained tenacious mucopurulent material, and the membranous lining was red and edematous. Because of this, the larynx, trachea, and bronchi showed reduction of the caliber of their lumen. A purulent, elastic exudate gave the appearance of a pseudomembranous lining.

FIG. 5 — (A) High power field of lung showing exudate obstructing bronchus, (B) distention of distal segment, (C) destruction of epithelial lining.

Microscopic examination. Sections from the lung showed that the small bronchi were filled with a purulent exudate, and the walls were diffusely infiltrated with polymorphonuclear leukocytes. In areas the epithelial lining was partially degenerated, and in others it was entirely missing. The small bronchi were edematous, and the blood vessels were congested. Surrounding these bronchi some of the alveoli were distended with purulent exudate, consisting chiefly of myriads of polymorphonuclear leukocytes and fibrinous material, together with degenerated epithelial cells. The alveolar walls were edematous and thickened, and in other places there was partial collapse of the alveolar structure. Then again, in some cases, the microscopic appearance showed the membranous lining to be absent, as if there were many small ulcerations. The smaller bronchi were filled with masses of inflammatory exudate, consisting chiefly of intact and partially degenerated leukocytes and fibrinous material. The walls of the immediately adjacent alveoli were somewhat thickened and showed evidence of inflammation. In some cases, there was partial collapse and atelectasis of the alveolar structure, presumably caused by the exudate within them. In still other cases the alveolar spaces were filled for the most part with a collection of polymorphonuclear leukocytes, and in some areas there were small patches of hemorrhage. In other areas, the alveoli were found in areas containing gross hemorrhages where the blood vessels were congested.

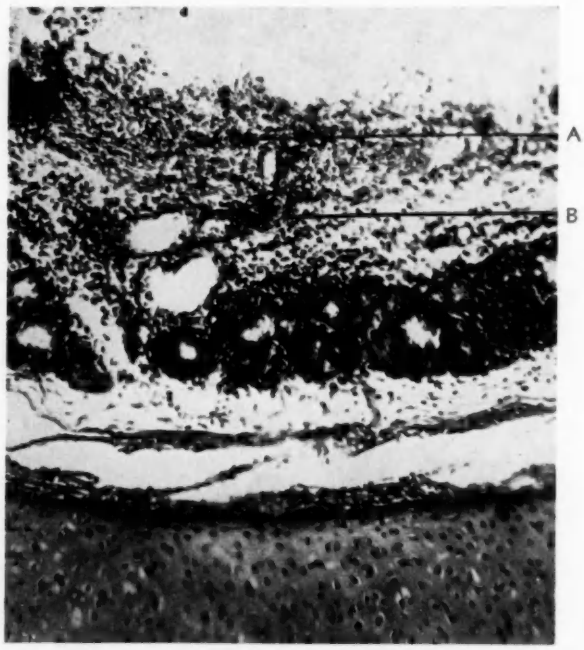


FIG. 6 — (A) Showing purulent exudate of a bronchus, (B) adherent to the bronchial wall with total destruction of underlying epithelium.

The findings at autopsy, in addition to confirming the bronchoscopic observations, revealed atelectatic and emphysematous areas, as well as bronchopneumonia. These findings attested further to the severity of the infection with its accompanying mucopurulent secretions and the resultant obstructive symptoms.

Further studies of the pathological changes in the tracheobronchial tree and the trial of systemic therapy with drugs are necessary to produce a sizeable reduction in the mortality rate.

SYMPTOMS

Acute laryngotracheobronchitis may be precipitated by an infection of the upper part of the respiratory tract, with its associated symptoms, following which fever soon develops. This sequence occurred in over half of our cases. The patients gave a history of having been sick on an average of three days before entering the hospital.

Patients with this disease are acutely ill. Their temperature ranges from 102 to 106 degrees F., their pulse rate is

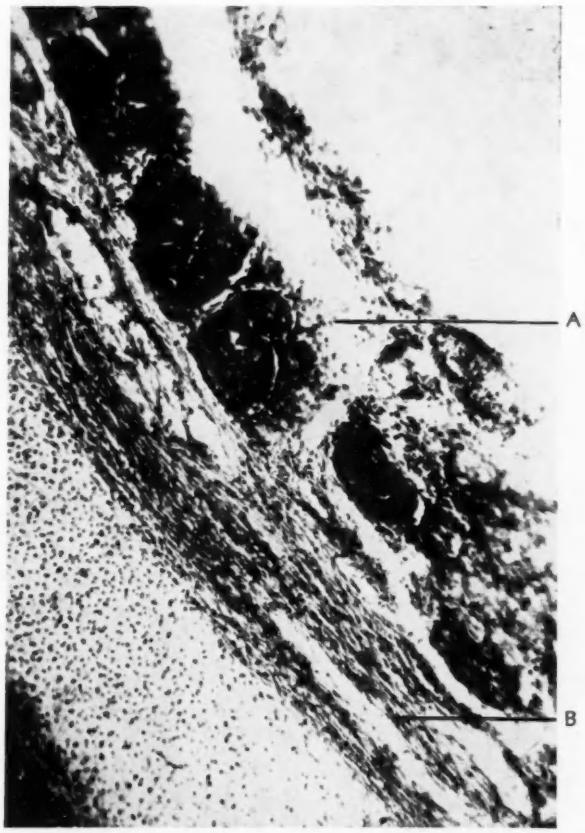


FIG. 7 — (A) Showing inflammatory lining wall of a bronchus with edema and destruction of epithelial layers beneath. (B) Edema and infiltration of polymorphonuclear leukocytes of subepithelial layers.

rapid, respiratory distress is marked, and they are toxic. In well over 50 per cent of the cases which we studied, hoarseness appeared early and was preceded or followed by a croupy cough, denoting subglottic involvement. Later, the hoarseness was accompanied by dyspnea with retraction, pallor, and sometimes, but not often, cyanosis. Dyspnea with retraction was noted in 47 cases.

In cases in which the infection is due to streptococcus the elevation of temperature is usually higher than it is in the staphylococcic type. At this stage, auscultory exmination of the chest may reveal that air is failing to enter the lungs due to obstruction of the bronchi by dry, crusted, mucous plugs.

As the disease progresses, the dyspnea becomes more severe, there is marked retraction of the suprasternal space, the supraclavicular space, and the epigastrium, and marked depression of the intercostal spaces appears, accompanied by pallor, restlessness, and sometimes, but not often, cyanosis.

The final picture is, as Richards[18] so ably describes it, "a ghastly spectacle of death by asphyxiation and suffocation," or, as we have termed it, "a peripheral asphyxia." Such is the usual course of the disease, unless some prompt, courageous treatment is instituted, and sometimes even then all efforts are futile.

FIG. 8 — (A) Showing lung with atelectasis and thickening of alveolar wall and infiltration with polymorphonuclear leukocytes. (B) Emphysema. (C) Purulent exudate in bronchus. (D) Destruction of bronchial epithelium.

DIAGNOSIS

Early diagnosis in cases of acute laryngotracheobronchitis is just as important as it is in any other disease if we expect to lower the mortality rate. From the number of cases reported here, it is obvious that this is a serious disease. The importance of making an early diagnosis is a paramount necessity when we consider that in our series the following diagnoses had been made by the physicians who sent the patients to the hospital:

Tonsillitis	1
Diphtheria	27
Croup	25
Foreign body	1
Whooping cough	5
Scarlet fever	1

The diagnosis of diphtheria tops the list; however, we think we can justly say that laryngeal diphtheria now can be considered a rare condition. Its onset may resemble that of laryngotracheobronchitis. However, nondiphtheritic laryngitis usually presents marked changes in the subglottic region, whereas laryngeal diphtheria, although it may be primary in the larynx, is more commonly an extension from the pharynx. In cases of diphtheria, direct smears from the laryngeal membrane[13] (which should be taken in all cases of laryngeal infection) invariably reveal diphtheria bacilli. In such cases, even though antitoxin is administered because diphtheria is suspected, it is imperative to supplement the treatment by either intubation or a

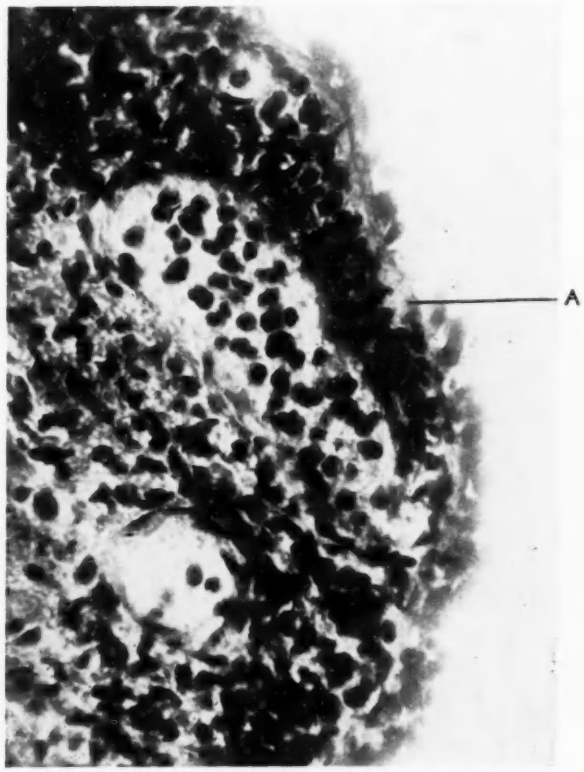


FIG. 9 — (A) High power field of bronchus, showing ulceration and partial destruction of epithelial lining.

tracheotomy. This is also extremely important in the treatment of acute laryngotracheobronchitis and, therefore, should be done early.

Our purpose is to define terms, giving the corresponding clinical picture; and to show the different stages and factors as the process develops involving the various anatomical areas, and finally the differential diagnosis.

TERMS, SYNONYMS, AND DEFINITIONS

Croup — Any affection of the larynx in children, characterized by difficult and noisy respiration and hoarse cough.

1. "Catarrhal Croup" or "Acute Catarrhal Laryngitis": Simple inflammation of the mucous membrane of the larynx.

2. "False Croup" or "Laryngitis Stidulosa" or "Spasmodic Laryngitis": Simple inflammation of the mucous membrane of the larynx accompanied by night attacks of closing of the glottis causing inspiratory stridor.

3. "Membranous Croup" or "Pseudomembranous Croup": Inflammation of the larynx in which there is a pseudomembranous exudate on the vocal cords.

4. "True Croup" or "Membranous Croup": Inflammation of the larynx caused by diphtheria bacillus.

5. "Spasmodic Croup" or "Laryngismus Stridulus" (no laryngitis):

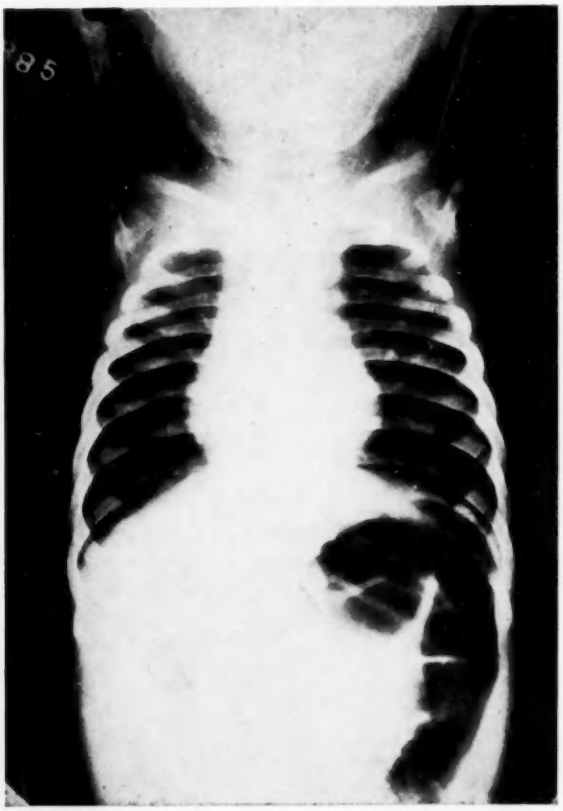


FIG. 10 — Case T. B., a 5 month old child. There is slight bilateral enlargement in the upper cardiac region with pressure on the trachea.

Spasmodic closure of the glottis, lasting a few seconds, followed by noisy inspiration and implying that there is no inflammation, as illustrated in tetany, breath-holding spells in convulsions, and in the paroxysms of whooping cough.

Acute laryngotracheobronchitis: Inflammation of the mucosa of the larynx, trachea, and bronchi.

We will select the three terms, "catarrhal laryngitis," "spasmodic laryngitis," and "laryngotracheobronchitis," since by definition they more accurately describe the disease responsible for the clinical picture. Because of common usage, however, the selection of the term "spasmodic laryngitis," instead of "spasmodic croup," is for the most part a technicality.

Before describing the symptoms, the course, and other factors which make for a differential diagnosis of these clinical entities, it must be stated that in the early stages of the process it is impossible to make this differential diagnosis. In many instances it is indeed difficult to know just where to draw the line, even after the patient is improved. An accurate and detailed history is very helpful. The fact is that a case beginning as catarrhal laryngitis or as spasmodic laryngitis may remain as such, or may progress to a laryngotracheitis or laryngotracheobronchitis.

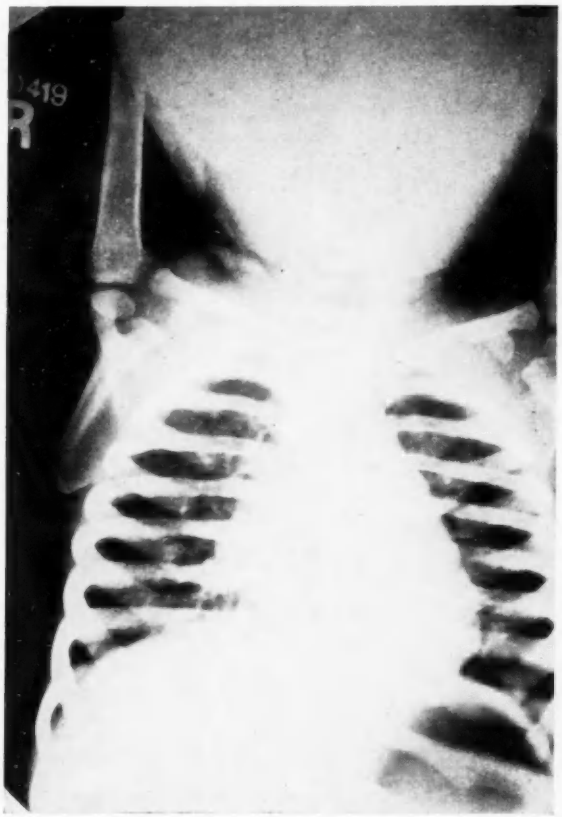


FIG. 11 — Case L. A., a 15 month old child. Both hila show increased density. The bronchial markings are slightly infiltrated throughout both lungs. There is no evidence of pneumonia.

CASE REPORTS

R. H., a 3½ year old boy, was admitted to the hospital April 22, 1940. The chief complaint was that of difficult breathing. The present illness started with infection of the upper part of the respiratory tract six days previously. Difficult breathing and a brassy cough developed on the morning of admittance. The child's temperature was 101.8 F., the pulse rate was 120, and the respiratory rate was 29. Physical examination revealed a well developed and well nourished boy, acutely ill, and in respiratory distress. His color was good except for slight circumoral pallor and flushed cheeks. There was a slight mucopurulent discharge coming from the nose. The soft palate and pharyngeal walls were inflamed. However, exudate or pus was not present. Laryngoscopic examination showed the entire laryngeal mucosa to be red and injected, and the cords were slightly thickened, but there was no exudate or membrane present. The cervical glands were not enlarged. Examination of the chest revealed respiratory embarrassment, and there was supra- and infrasternal retraction with each inspiration. The intercostal spaces also retracted slightly. Auscultation revealed harsh breath sounds. Rales were not heard. There was a slight croupy, brassy inspiratory sound when the patient cried

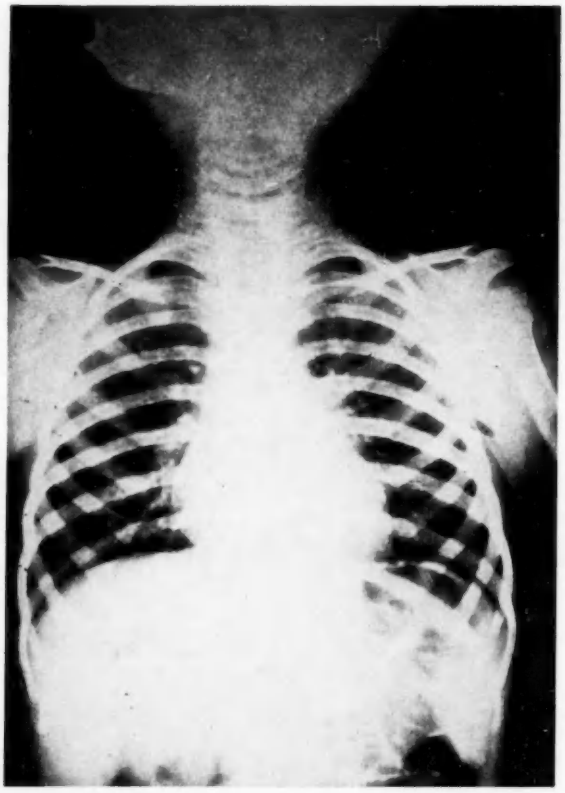


FIG. 12 — Case E. H., a 2½ year old child. Both hila show increased density. The bronchial markings are slightly infiltrated throughout both lungs. There is no evidence of pneumonia.

or was disturbed. Further examination revealed no positive findings. The following day, April 23, 1940, the patient's general condition was markedly improved, and only slight respiratory embarrassment was evident. Blood examination revealed hemoglobin 61 per cent, erythrocytes 3,720,000, and leukocytes 12,800 with polymorphonuclear neutrophils 82 per cent and lymphocytes 18 per cent. There were 4 band forms and 78 segmented forms. The urine showed an acid reaction, contained a trace of albumin, no glucose, 4 plus acetone, no diacetic acid, had a specific gravity of 1.025, and was normal on microscopic examination.

On April 24, 1940, the child was breathing easily and there was retraction. However, his voice continued to be slightly croupy, and he continued to have an occasional hoarse cough. On April 25, 1940, the patient's temperature rose to 100.4 F., but it subsequently returned to normal, and there were no further symptoms. He was discharged from the hospital on April 30, 1940.

The clinical picture of "spasmodic laryngitis" is illustrated by the case of B. C., a 4 year old boy, who was admitted to the hospital at 2 a.m., April 4, 1940. The patient had suddenly awakened because of difficulty in breathing and a brassy cough. Physical examination revealed a well developed, healthy appearing child, who was in acute distress due to difficulty in getting air into his lungs. There were suprasternal, infrasternal, and intercostal retractions. The child did not appear toxic or fatigued. However, there was some cyanosis of his lips and fingernails. The temperature was 99 F., the pulse rate was 155, and the respiratory rate was 43. The tonsils were enlarged. The fauces and pharyngeal walls were moderately inflamed, but membrane, exudate, or pus was not present. Ausculation of the chest revealed a loud, harsh sound over the larynx, trachea, and large bronchi. Rales were not heard. The blood and urine were normal. Two drams of syrup of epecac were given, following which the child vomited and became somewhat relieved. The temperature, pulse rate, and respiratory rate at 4 a.m. were 98.6 F., 115, and 40, respectively. By 8 a.m., the respiratory rate had diminished to 25. The child made an uneventful recovery.

Laryngoscopic examination in these cases reveals normal findings except during the spasm, when there is discoloration of the laryngeal mucosa varying from lavender to bluish, as is expected in any type of spasm.

The characteristics of "laryngotracheobronchitis" are illustrated in the case of P. C., a 23 month old child who was referred to the hospital on February 18, 1940. A diagnosis of croup and obstructive pneumonia had been made. The child had suddenly become ill two nights previously when breathing became difficult.

Examination revealed a well nourished male infant, acutely ill and struggling to breathe. There was slight cyanosis of the lips and the nails and a pallor about the face. There was suprasternal and infrasternal retraction. The voice was fairly good. Some dried secretion was seen about the anterior nares. Only moderate congestion of the tonsils and pharynx was present. The breath sounds were harsh, but rales were not heard.

Direct laryngoscopic examination revealed an acutely inflamed laryngeal mucosa with subglottic edema. Membrane or exudate was not present. The temperature was 103 F., the pulse rate was 144, and the respiratory rate was 40. Examination of the urine revealed a trace of albumin and 2 plus acetone. Blood examination revealed hemoglobin 65 per cent, erythrocytes 3,540,000, and leukocytes 12,400 with polymorphonu-

clear neutrophils 70 per cent, lymphocytes 28 per cent, and monocytes 2 per cent. During the first three hours of observation, the child showed no response to treatment and became exhausted. A low tracheotomy was performed, following which there was immediate relief. Shortly after the tracheotomy had been performed, the breathing became regular, the skin a healthy pink, and the child slept. By the fourth postoperative day, the temperature had returned to normal. Recovery was uneventful.

"Laryngotracheobronchitis," running a less fulminating course, is noted in the case of S. W., a nine month old infant, who was admitted to the hospital at 1 a.m. on October 19, 1939. Four days previously he had had a sudden attack of croup at 4 a.m. During the following two days there had been alternate periods of difficult breathing and apparent relief. During the next two days there had been no relief. Physical examination revealed a well developed child who was having difficulty with respiration and appeared markedly fatigued. There was suprasternal and infrasternal retraction and a loud laryngeal crow. The skin was pale. The pharynx was moderately inflamed, but exudate or membrane was not present. Laryngoscopic examination revealed a red, swollen laryngeal mucosa which contained a large amount of greenish exudate. The exudate was aspirated, and a smear was taken from the laryngeal membrane from which a culture was made. The breath sounds were harsh, but rales or dullness was not elicited. The temperature was 102.4 F., the pulse rate was 170 (questionable), and the respiratory rate was 65. By 9 a.m. the child's condition was the same, and it was evident that an operative procedure was necessary. A one month O'Dwyer tube was inserted, following which there was considerable relief. During the next five days the patient was fairly comfortable, but some toxemia persisted, as revealed by the temperature which varied from 101 to 103, with a downward trend. Likewise the pulse rate varied from 140 to 160 and the respiratory rate from 40 to 50.

Blood examination revealed hemoglobin 62 per cent, erythrocytes 3,360,000, and leukocytes 13,700 with polymorphonuclear neutrophils 66 per cent, lymphocytes 26 per cent, monocytes 6 per cent, and plasma cells 2 per cent. The blood picture remained practically the same until two days postoperatively when the leukocyte count was 23,650. The urine was normal. On October 20, 1939, after having worn the intubation tube for six days, the child coughed up the tube, following which he immediately became dyspneic and cyanotic. The tube was reinserted after which there was relief. A low tracheotomy was performed a few hours later. The patient's reaction to this procedure was moderate, the temperature rising to 103 F. However, by the third postoperative day he appeared to be making an uneventful recovery. The tracheotomy tube was removed on December 1, 1939. The patient was discharged from the hospital on December 6, 1939, at which time the wound was healed.

RESUME OF CASES

A resume will include the following physical signs of acute laryngotracheobronchitis:

1. A healthy individual who has developed an illness of sudden onset, preceded or accompanied by an infection of the upper part of the respiratory tract, whose tonsils and pharynx usually are congested, and whose glands are somewhat involved.
2. The heart action as a rule is of good quality; however, in some patients the pulse rate is irregular.
3. As the infection increases, the larynx becomes affected, and this is in-

dicated by hoarseness or a croupy cough and increased respiratory difficulty.

4. Retraction at first is slight, then it rapidly becomes more severe.
5. The patient becomes critically ill, toxic, and restless.
6. Pallor and later cyanosis develop.
7. The picture is that of rapidly progressing respiratory asphyxia.

TREATMENT

The attending physician always should bear in mind that acute laryngeal obstruction in a child is potentially acute laryngotracheobronchitis until proven otherwise. Too often this so frequently fatal disease is diagnosed as diphtheria, spasmodic laryngitis, or catarrhal laryngitis, and only when the child is dying does the physician realize the gravity of the condition.

The efficient care of patients suffering from acute laryngotracheobronchitis depends upon a well trained hospital personnel consisting of a readily accessible and competent bronchoscopist, experienced residents on call at all times, and especially trained internes and nurses. It is essential that these patients

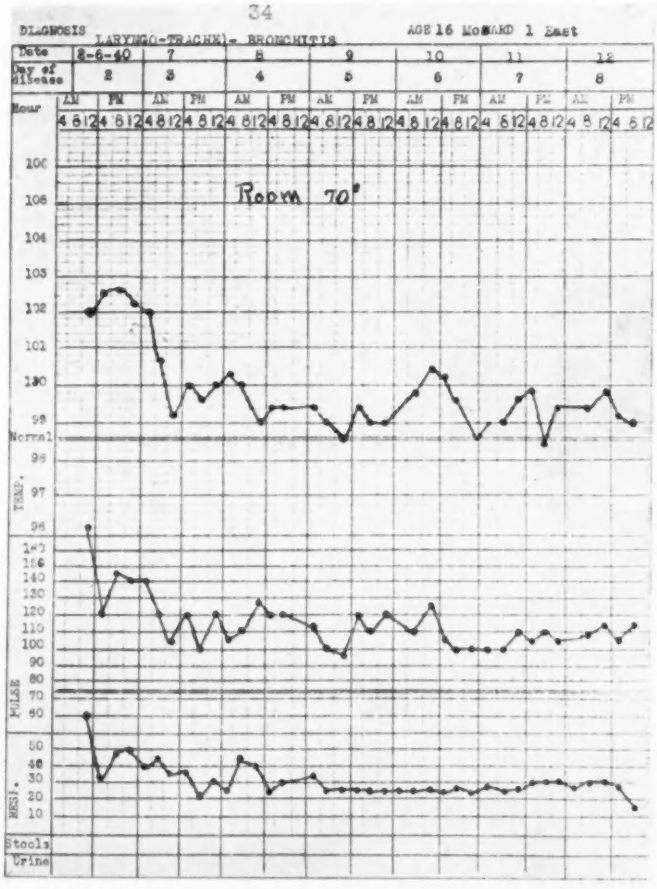


FIG. 13 — Temperature chart of a 16 month old child. This shows a drop in temperature after placing the patient in a humidified room.

be under constant observation, for a change may suddenly occur and a fatal outcome result unless immediate proper treatment is instituted. Any child with continuous signs of laryngeal obstruction should be sent to a hospital which has a personnel capable of properly handling a patient in this condition, rather than an endeavor made to treat the patient at home.

On admission to the Essex County Isolation Hospital, the patient is seen by the resident physician. When definite laryngeal obstruction is noted, a laryngoscopic examination is done and smears are taken from the laryngeal membrane from which cultures are made for diphtheria and other types of organisms. This laryngoscopic examination is helpful in several ways. It enables us to determine whether or not suggestive diphtheritic membrane is present and at the same time the amount of swelling present in the subglottic area can be observed.

If the patient's condition is such that some operative procedure is not immediately necessary for relief of the obstructive symptoms, he is then placed in a room supersaturated with moisture at a temperature of about 70 degrees F. In our hospital we are able to obtain this moisture by letting hot water run into the tub in the bathroom adjoining the patient's room. More recently we have used a Walton humidifier, and have found it very satisfactory. We feel that the entire room supersaturated with moisture is far better than the old croup tent, as the patient is more comfortable and he is able to obtain more oxygen. This procedure facilitates observing and caring for the patient. The value of treatment by supersaturating the air with moisture is of course to make the patient more comfortable, and to help him to

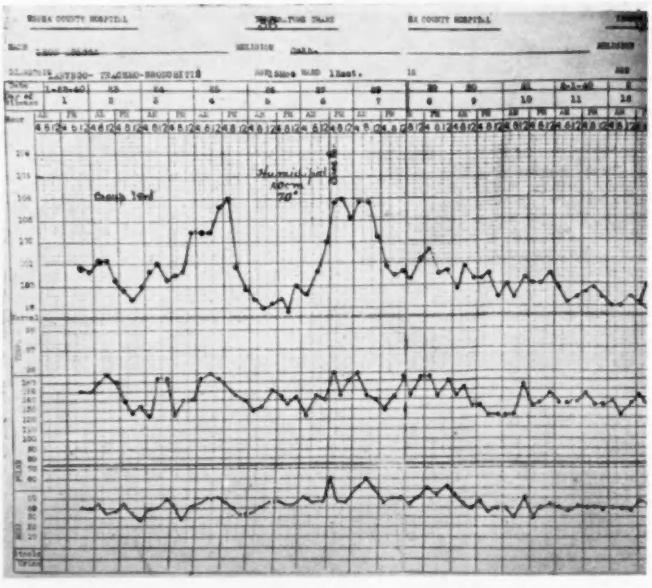


FIG. 14 — Temperature chart of a 15 month old child with acute laryngotracheobronchitis who was placed in the croup tent at first. Note the elevation of temperature until after the patient was placed in the humidified room, when the temperature dropped. This was followed by a tracheotomy, and note the slight reaction following this procedure while the patient was in the humidified room.

breathe easier. It also prevents dehydration. These measures aid in keeping gummy, tenacious exudate from drying and crusting, and in liquifying it as much as possible so that it may be expelled more easily.

It is doubtful if medicated inhalations have any real value in the treatment of this disease, however time honored in usage they may be.

It has been our custom to give these patients iodides in some form.

Opiates and belladonna are strongly condemned. Opiates further dull the cough reflex and produce an insidious restfulness which sometimes is the harbinger of death. Belladonna and atropine serve to make the secretion, which we wish to liquify, only drier.

Adequate fluid intake is necessary for the patient. This can usually be taken in sufficient amounts by mouth, but it may be necessary to administer it by clyses or by intravenous injection. Soft and liquid foods in adequate amounts can usually be taken by mouth.

When it becomes apparent that the patient is not improving with these palliative measures, as shown by increasing dyspnea, then some operative procedure

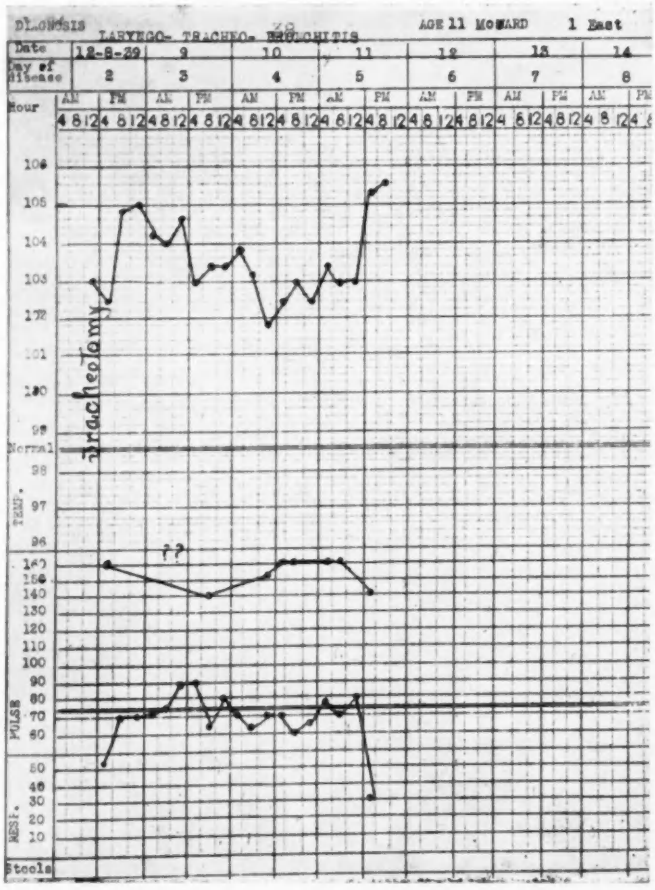


FIG. 15 — Temperature chart of a 11 month old child suffering from acute laryngotracheobronchitis.

must be considered. Greater respiratory distress is manifest by increased restlessness and suprasternal and infrasternal reactions, and is revealed by examination with the stethoscope which elicits very little air entering the lungs. When the respiratory effort has been so great that the patient has become exhausted, restlessness decreases, an ashen pallor occurs, rather than a cyanosis, and the patient, resigned to his fate, appears to give up the struggle for life.

Every patient with sufficient laryngeal or tracheal involvement to cause any audible stridor on exertion is considered in the danger zone.[16] If the stridor is noticeable when he is resting, tracheotomy should be considered. If it is audible when he is asleep, the operation is urgently required. In a vast majority of our cases, this condition was present when the patient was admitted to the hospital. When dyspnea is severe, immediate intubation or tracheotomy is necessary. The question of importance is, "What operative procedure should be employed?" Aspiration through the bronchoscope may give temporary relief, but this usually will have to be repeated often and requires the constant services of the bronchoscopist. Intubation may be done quickly and usually gives immediate relief, unless there is also supraglottic edema. However, in our experience intubation has definite disadvantages, except as a temporary measure for relief until tracheotomy can be done.

With intubation alone, we have been successful in certain cases as far as the immediate infection is concerned, but we have observed a complication in the form of chronic laryngeal stenosis which eventually has necessitated a tracheotomy.

You might ask, "Why then is tracheotomy not done in all cases?" No surgeon would think of operating on a patient who is in shock, but he would first attempt to bring about a reaction. We must remember that there is a condition known as respiratory shock. For instance, a patient has been suffering from acute respiratory distress for several days and is brought into the hospital well-nigh exhausted. We find that if it is possible for this patient to rest for a few hours by being placed in a humidified room and by having intubation carried out, he will tolerate tracheotomy better than if it were performed immediately.

We prefer tracheotomy as the operative procedure of choice. It must be remembered, however, that when relief from the immediate respiratory distress is obtained, only a part of the victory is won. Simpson[19] states that pneumothorax is a serious complication in laryngotracheobronchitis. Fortunately, we have not seen this complication as a result of, or coincident with, tracheotomy. Formerly, we placed these tracheotomized patients in a croup tent in which the air was moist, but hot. Last winter we placed these patients in a humidified room in which the temperature was kept at 70 degrees F. By doing so, we found that they, as well as patients upon whom tracheotomy or intubation was not necessary, got along far better than patients who had been placed in a croup tent.

At this point I wish to give credit to Dr. F. W. Davison[7] for first reporting this method of treatment before the Eastern Section of the Triological Society, and the following information concerning the air conditioning of an oxygen tent is taken from a personal communication from him:

> I suspect that the therapy of many diseases could be improved by affording the patient certain combinations of temperature, humidity, and air flow.
>
> For the treatment of acute laryngotracheobronchitis, we use an oxygen tent canopy rather than an entire room for the reasons that (1) my own supersaturated room causes walls to drip with moisture, and (2) paint and furnishings become ruined by moisture.

To obtain a high humidity without high temperature we use a Walton humidifier.

When using a tent, comfortable climatic conditions should be supplied. The temperature and humidity within the canopy affect the comfort of the patient more than the concentrations of oxygen and carbon dioxide.

The problem here is to add water vapor to the canopy more readily than it is removed by the cooling chamber. By using a humidifier which evaporates one pint of moisture per hour, we have been able to keep the relative humidity at 95 per cent, with a temperature of 70 degrees F., which is entirely comfortable. On the other hand, if a steam generator is connected to the canopy, conditions such as are present in the average so-called croup tent are produced, namely, temperature of 90 degrees F. and a relative humidity of 95 per cent, that is, an effective temperature index of 80 degrees F. This is an exceedingly oppressive and uncomfortable condition. Yet, for generations youngsters suffering from croup have been subjected to these conditions without consideration for their comfort. We should not lose sight of the fact that perspiration can cause excessive fluid loss. Conversely, raising the humidity while keeping the temperature low enough to avoid perspiration is a means of conserving the body's supply of fluids. Thus, maintaining a high humidity with a temperature of not more than 70 degrees F. can be a useful method of conserving body fluids so that an adequate volume will be available for kidney function.

The postoperative care of the tracheotomized child is perhaps the most important factor in his ultimate recovery. The patient is placed in a vapor-laden room kept at a temperature of 70 degrees F. and is constantly cared for by a qualified nurse especially experienced in this work. Through the tracheotomy tube, suction of the obstructing tracheal secretions frequently and effectively can be done with a rubber catheter attached to a suction machine. Solutions, such as normal saline, sodium bicarbonate, or 1 per cent monochlorophenol, may be instilled into the trachea to soften these secretions so that they may be easily coughed up or aspirated by suction. The bronchoscope may be inserted through the tracheotomy wound to secure effective aspiration if obstruction persists despite frequent aspirations by catheter. When intubation is used, such procedures are not possible.

At the Essex County Isolation Hospital, during the past fourteen months 16 children were tracheotomized in whom a diagnosis of laryngotracheobronchitis had been made. Five of these children died, giving a mortality rate of 31 per cent. It must be expected that these patients will have a stormy course following tracheotomy, and it is only under the most skilled and assiduous care of a trained and conscientious personnel that the mortality rate can be kept at the lowest point.

In the treatment of staphylococcic infections, the problem is to keep the bronchi as moist as possible so as to enable the patient to expectorate the secretion. Here, Evans[8] advocates the use of a staphylococcus bacteriophage and reports good results. The primary action is liquification of the staphylococcus. The use of staphylococcus bacteriophage, therefore, has some rational basis, but as yet we have not used it.

Difficulty in maintaining an adequate air way in cases of acute laryngotracheobronchitis, even after tracheotomy, commonly results from obstruction of the trachea and bronchi caused by thick or inspissated secretion. The bronchoscope must be resorted to for removal of such secretions.

Cassidy[4] reports a case in which the secretions were aspirated with the bronchoscope thirty-seven times over a period of thirteen days. Galloway[10] advocated postural drainage as an adjunct, which has proven especially valuable. The head of the patient is lowered, and the bronchial lumina are kept free of secretion and plugs by suction applied through the tracheotomy tube.

Sulfanilamide and sulfapyridine were used in conjunction with some mechanical aid in 23 cases in our series.

In our opinion, these drugs may help in certain cases, but they are not a specific for this disease. In the treatment of any disease, rational therapy is based upon a fundamental knowledge of the pathology of that disease.

AUTOPSY REPORTS

Autopsy No. 1 was of a 19 month old colored male child, in whose case a clinical diagnosis was made of acute laryngotracheobronchitis. Postmortem examination disclosed a well developed and well nourished child. The pericardium contained a moderate amount of air or gas. The heart was slightly dilated, but was otherwise normal. The larynx and trachea were moderately congested and were filled with frothy fluid. The main and smaller bronchi were also congested and were filled with frothy fluid. The lungs were congested and edematous, and considerable frothy fluid exudated on cut section. The thymus was slightly larger than normal, but apparently caused no obstruction. The abdominal organs appeared normal with the exception of the spleen which showed hyperplasia of the malpighian corpuscles.

Microscopic examination showed the mucous membrane of the larynx to be ulcerated and necrotic, and the entire mucosa and submucosa to be edematous and infiltrated with polymorphonuclear leukocytes. The epithelial layer of the mucosa of the trachea was densely infiltrated with pus. In some places there was necrosis. Purulent, necrotic exudate gave a pseudomembranous appearance. The entire mucosa and submucosa of the trachea were edematous and were infiltrated by polymorphonuclear leukocytes. The vessels of the submucosa were congested. The sections from the bronchi revealed the same pathologic changes as those from the trachea. The lungs showed some exudate in the bronchioles and a zone of purulent infiltration in and around the bronchiole walls. The alveoli surrounding the bronchioles were filled with purulent exudate in typical lobular pneumonic distribution.

Diagnosis: Acute laryngotracheobronchitis; acute bronchopneumonia.

Autopsy No. 2 was of a 14 month old white male child, in whose case a clinical diagnosis was made of tracheobronchitis and bronchopneumonia. Postmortem examination revealed a very well nourished, fairly well developed child. The skin appeared pale and wax-like and suggested considerable subcutaneous edema, although there was no true pitting. The skin was clear, and contained no rashes or discolorations. The head was symmetrical. The anterior fontanelle admitted just a finger tip. The tension was normal. There was no external evidence of discharge from the ears. The pupils were equal, and there was no evidence of conjunctivitis. The anterior nares contained a small amount of dried, crusted, mucopurulent material. The lips were somewhat dry. There was no discharge from the mouth. The cranial cavity was not examined. The chest was symmetrical. There was no flaring of the ribs or beading of the costochondral junctions. The thymus was normal in size and position, and it did not compress the trachea. The cut surface of the thymus was normal. The

larynx and trachea showed no evidence of obstruction to the air way. The mucosa was red, somewhat edematous, and appeared moist, but there was no actual exudate. The bronchi were red and congested, and the walls were edematous so that their lumina were slightly decreased in caliber. They contained a considerable amount of thin, reddish fluid. The pleural surfaces were smooth and glistening, and the pleural cavities were free of fluid. There was a small area of red consolidation at the apex of the upper lobe of the right lung. Here, the parenchyma of the lung was firm and congested. A similar area was observed in the upper portion of the lower lobe of the right lung. The left lung was rather congested and edematous, but was well areated throughout. The glands at the hila and those along the trachea and larger bronchi were slightly enlarged and appeared congested. The pericardial cavity contained no free fluid, and the epicardial surface was smooth and glistening. The chambers of the heart were not dilated. The free edges of the valves were thin, and the valves appeared competent. The endocardial surface was pale and smooth, and gross scarring of the myocardium was not seen. The abdominal organs and genito-urinary organs appeared normal.

Microscopic examination of the mucous membrane of the trachea revealed edema and diffuse infiltration of polymorphonuclear leukocytes. It was degenerated in some areas and in others it was absent as if many small ulcerations were present. The glands were enlarged and appeared overactive, and in some areas their acinic structure was destroyed. Secretions from the lungs showed intense congestion and edema about the smaller bronchioles, the walls of which were swollen and diffusely infiltrated with many polymorphonuclear leukocytes. Their lumina were filled with masses of inflammatory exudate consisting chiefly of intact and partially degenerated leukocytes and fibrinous material. The walls of the immediately adjacent alveoli were somewhat thickened and showed evidence of inflammation. In other areas partial collapse and atelectasis of the alveolar structures had taken place, presumably from the exudate within the terminal bronchi. Sections were not taken from the areas of consolidation in the upper and lower lobes of the right lung which were noted in the gross examination.

Diagnosis: Laryngotracheobronchitis with obstruction due to liquid exudate; bronchopneumonia of the upper and lower lobes of the right lung.

Autopsy No. 3 was of a 6 year old white male child, in whose case a clinical diagnosis was made of diphtheria. Postmortem examination revealed a well developed and well nourished child. The skin was clear and showed no rashes or discolorations. There was no edema or evidence of recent weight loss. The head was well formed, and the scalp was clear. There was no external evidence of discharge from the ears. The pupils were equal, and there was no conjunctivitis. The anterior nares contained a small amount of dried mucopurulent material. The cranial cavity was not examined. There was no beading of the costochondral junctions. A moderate amount of subcutaneous fat was present. The thymus appeared to be normal in size and position, and it did not compress the trachea. The cut section of the thymus was normal. The pleural cavities contained no free fluid. The pleural surfaces were smooth and glistening. The parenchyma of the lungs were somewhat congested and contained a small amount of thin, sanguineous fluid, but there was no gross evidence of consolidation, and the lungs were well areated throughout. The smaller bron-

chioles were red and injected and contained a moderate amount of glary, bloody material. The glands at the hila and along the large bronchi and trachea were enlarged and somewhat congested. The mucosa of the larynx, trachea, and large bronchi was swollen, hyperemic, and edematous. Covering this surface through nearly its entire extent there was thick, somewhat adherent, mucopurulent exudate which separated easily from the underlying tissues and left no gross area of erosion. The pericardial sac contained no fluid. The epicardial surface was smooth and glistening. The chambers of the heart contained a small chicken-fat clot but were not dilated. The free margins of the valves were thin and appeared competent. Gross scarring of the myocardium was not present. The abdominal organs were normal with the exception of the liver which was greatly enlarged and extended from 1 to 2 inches below the costal margin. It was congested, but soft, and its cut surface showed reddening and hyperemia of the central areas, and the large veins were filled with blood. The kidneys were congested, and the vessels appeared dilated, but the capsule was delicate and stripped easily. The cut surface showed some prominence of the glomerular markings.

Cultures made from smears taken from the trachea, bronchi, and larynx were negative for diphtheria. The predominating organism was staphylococcus aureus hemolyticus. Diplococci, pneumococcus type III, and nonhemolytic streptococcus were also present. Microscopic sections were not taken.

Diagnosis: Acute laryngotracheobronchitis.

Autopsy No. 4 was of a 11 month old white male child, in whose case a clinical diagnosis was made of acute laryngotracheobronchitis. Postmortem examination revealed a well developed and very well nourished child. The skin was clear, and revealed no rashes or discolorations. A recent tracheotomy wound was present in the lower portion of the neck, situated about one inch above the jugular notch. The edges of the wound were slightly reddened and edematous, but there was no evidence of infection or emphysema of the surrounding structures. The head was symmetrical. The anterior fontanelle was open, admitting a finger tip. It was not depressed. There was no external evidence of discharge from the ears. The pupils were equal, and there was no conjunctivitis. Some greyish, dried, crusted matter lay just within the nares. The cranial cavity was not examined. The chest was symmetrical. There was no flaring of the ribs or beading of the costochondral junctions. A moderate amount of subcutaneous fat was present, but no edema. The pleural cavities were free of fluid, and the surfaces were smooth. Scattered throughout all lobes of both lungs were small areas of patchy consolidation where the surface appeared red and congested. The smaller ramifications of the bronchial tree contained tenacious, mucopurulent material, and the mucosa was red and edematous. Elsewhere the lungs were well aerated. The glands at the hila and along the bronchi and trachea were congested and hyperemic. The larynx, trachea, and main bronchi showed swelling and hyperemia of the mucosa, with some reduction of the caliber of their lumina. In many places purulent, plastic exudate had formed which gave the appearance of a pseudomembrane to these structures. The pericardium contained 3 to 4 c.c. of straw colored fluid, but the epicardial surface was glistening and a minimal amount of fat lay beneath it. The chambers of the heart were not dilated, but contained a postmortem clot. The free margins of the valves were thin, the papillary muscles were not thickened, and the valves appeared

competent. The myocardium showed no gross scarring. The thymus was not enlarged, and its cut surface was normal. The abdominal organs and genito-urinary organs appeared normal.

Microscopic examination of the lungs showed the small bronchi to be filled with purulent exudate and the walls to be diffusely infiltrated with polymorphonuclear leukocytes. In areas the epithelial lining was partially degenerated and in others entirely missing. These structures were edematous, and the blood vessels were congested. Surrounding these bronchi, the alveoli were distended with purulent exudate consisting chiefly of myriads of polymorphonuclear leukocytes and fibrinous material, together with degenerated epithelial cells. The alveolar walls were edematous and thickened, and in some areas partial collapse of the alveolar structure had taken place.

Diagnosis: Acute laryngotracheobronchitis; bronchopneumonia.

Autopsy No. 5 was of a 2 year old white male child, in whose case a clinical diagnosis was made of foreign body in the trachea. Postmortem examination revealed a well developed and well nourished child. The skin was clear and showed no rashes or discolorations. A recent tracheotomy wound was present which was about 2 inches long and lay about 1 inch above the manubrium sterni. The edges of the wound were somewhat red and edematous, but gross evidence of infection was not present. The underlying structures appeared to be free of infection. The head was well formed. The anterior fontanelle was closed. There was no external evidence of discharge from the ears. The pupils were somewhat constricted, but were of equal size. There was no injection of the conjunctivae. A small amount of dried, greenish material was noted in the anterior nares. The lips were dry and moderately fissured. The cranial cavity was not examined. The chest was well formed. There was no beading or flaring of the ribs. The pleural cavities contained a minimal amount of clear, straw colored fluid (10 to 15 c.c.). Adhesions were not noted, and the pleural surfaces were smooth and glistening. The lungs appeared edematous and congested, and on section contained a moderate amount of thin, watery, sanguineous exudate. There was no evidence of pneumonic consolidation. The lymph glands about the hila and along the bronchi and trachea were congested and slightly enlarged, but were not discolored. The larynx and trachea were edematous, hyperemic, and appeared acutely inflamed. The vocal cords were red and showed minimal thickening, but the air way appeared adequate. Below this region there was a greenish, plastic exudate which completely lined the lowermost portion of the larynx. Beneath this, the mucosa was red and hyperemic, but apparently intact, and gross erosions were not present. Lower down, the trachea and bronchi showed a pseudomembranous inflammation of the mucous membrane. The material was tenacious, thick, and dirty grey-green in color, and was moderately adherent to the mucosa. Upon removing it, the underlying structures were found to be intensely red, congested, and edematous. In the smaller ramifications of the bronchial tree there was an occasional area which appeared to be nearly obstructed, but there were no true areas of atelectasis surrounding them. The mediastinal tissues were edematous and showed evidence of emphysema, which apparently originated at the site of the tracheotomy wound. The pericardial sac was free and contained no fluid. The heart was not enlarged. The epicardium was smooth, and the myocardium showed no evidence of fibrosis. The ventricular chambers contained a small postmortem clot. The

valves were thin and delicate, and appeared competent. The papillary muscles were not thickened. The abdominal organs were normal with the exception of the spleen which showed minimal congestion, but it was not enlarged. The genito-urinary organs were normal.

Cultures made from smears of the larynx and trachea were negative for diphtheria. They showed staphylococci, streptococci, and gram-negative (otherwise unidentified) bacilli.

Diagnosis: Acute laryngotracheobronchitis.

Autopsy No. 6 was of a 6 month old white male infant, in whose case a clinical diagnosis of diphtheria (?) had been made. Postmortem examination revealed a moderately well developed, fairly well nourished child. The skin was clear, and showed no evidence of rashes or discolorations. The head was well formed. The anterior fontanelle was open and measured about 1 by 1½ cm. It was slightly depressed. There was no external evidence of discharge from the ears. Moderate crusting and a small amount of purulent material was present in the anterior nares. The eyes were clear, and there was no conjunctivitis. The cranial cavity was not examined. The chest was symmetrical. There was no beading or flaring of the ribs. The thymus appeared to be enlarged, particularly in the anteroposterior diameter, and compressed the trachea posteriorly. The thymus weighed 11 grams and on section was found to be normal. The posterior pharyngeal wall was moderately injected and somewhat edematous. The larynx, while slightly reddened, did not appear to be abnormal otherwise. The vocal cords were smooth and were not swollen. There appeared to be no obstruction of the air way at this point. Just below the larynx (½ inch) was an area of marked constriction of the trachea so that the caliber of the lumen was definitely decreased. At this point, the mucosa was reddened and slightly thickened. The larger bronchi contained only a small amount of mucoid and mucopurulent material. The smaller bronchi and terminal bronchioles were diffusely reddened. The mucosa was injected and edematous and partially covered by moderate amounts of stringy, mucopurulent, somewhat adherent exudate. The lungs were well areated throughout and showed no areas of consolidation or scarring. The perihilar glands and those along the trachea and bronchi were not enlarged or discolored. The pericardial sac was free and contained no free fluid or adhesions. The pericardial surface was smooth and glistening throughout. The heart contained a small postmortem clot. There was no dilatation of the ventricular chambers. The myocardium showed no gross scarring, and the endocardial surface was smooth everywhere. The free margins of the valves were thin and appeared competent. The aorta was normal. The abdominal organs appeared normal except for an accessory spleen which measured 1x1 cm. The spleen itself was not enlarged or congested. The genito-urinary organs were normal.

Diagnosis: Congenital atresia of trachea; acute pharyngotracheobronchitis.

Autopsy No. 7 was of a 21 month old white male child, in whose case a clinical diagnosis of laryngotracheitis had been made. Postmortem examination revealed a well developed child, in whom moderate evidence of dehydration was present. The skin was clear, and showed no rashes or discolorations. The pleural cavities did not contain any free fluid, adhesions were not noted, and the pleural surfaces were smooth and glistening. Both lungs showed diffuse areas of patchy consolidation, the cut surface being red, firm, and appearing acutely con-

gested. The posterior portion of the lower lobe of the right lung was entirely consolidated and partially atelectatic. The cut surface was dark red, hard, somewhat depressed, and more homogenous than the surrounding tissues. The glands at the hila, about and above the bifurcation of the trachea, were enlarged and congested. The mucosa of the larynx and trachea was hyperemic, edematous, and in several small areas definitely hemorrhagic. There was a definite constriction at the junction of the lower end of the larynx and the trachea. At this point some erosion of the mucosa and underlying structures was noted which was possibly due to attempts at intubation. There was marked swelling and edema of all the structures so that the tracheal lumen was encroached upon and became moderately constricted. The pericardial surface was smooth and glistening. The pericardial cavity contained about 5 c.c. of clear, serous fluid. The gross appearance of the heart was normal. The valves were free and appeared to be functionally adequate. Scars were not seen in the myocardium. The right side of the heart was dilated and was filled with a postmortem clot. The thymus weiged 14.7 grams and was normal on section. The pupils were somewhat constricted, but they were equal. The conjunctivae were clear. There was no external evidence of discharge from the ears. The anterior nares contained a small amount of purulent material. The cranial cavity was not examined. There was no free peritoneal fluid in the abdomen. The liver was somewhat distended and slightly congested, but on section presented the customary markings. The other adbominal organs were normal. The kidneys were slightly congested, but the capsules stripped easily and on section were normal. Otherwise, the genito-urinary organs were normal.

Microscopic examination of the lungs revealed large and small areas of purulent bronchopneumonia. The alveolar spaces were stuffed for the most part with collections of polymorphonuclear leukocytes, and in some areas small patches of hemorrhage were present. The alveolar walls were edematous and thinned out, but ruptured alveoli were not seen. The terminal bronchioles were filled with masses of inflammatory exudate, and in many areas the mucosa was absent. The underlying structures were diffusely infiltrated with numerous polymorphonuclear leukocytes, and some early fibroblastic reaction was noted. Section from the lobes of the right lung showed collapsed alveoli with a few areas containing gross hemorrhages. The blood vessels were distended. The smaller branches of the bronchial tree contained inflammatory exudate, but in some areas they were relatively clear and the lining appeared to be intact, though even in these areas minimal infiltration of the bronchial walls with inflammatory cells was noted.

Diagnosis: Acute laryngotracheobronchitis; bilateral bronchopneumonia.

CONCLUSIONS

1. An analysis of 62 cases of acute laryngotracheobronchitis with autopsy findings in 8 cases has been submitted.
2. Acute laryngotracheobronchitis in young children is a very important problem both for the general practitioner and the pediatrician.
3. Proper handling of these cases requires early recognition of the disease, and valuable time should not be lost in treating the patients with antitoxin when signs of obstructive dyspnea appear.
4. When acute laryngotracheobronchitis is suspected, the patient immediately should be transferred to

a hospital where direct laryngoscopy and bronchoscopy can be carried out at once, where active treatment, such as intubation and tracheotomy, may be instituted at a moment's notice, and where an especially trained personnel is always immediately available.

5. If time permits, x-ray studies should be made prior to the operation, otherwise they should be made immediately following the tracheotomy.
6. Intubation should be done for immediate relief only, and should be followed by tracheotomy.
7. Patients should be placed in a room supersaturated with moisture in which the constant temperature is 70 degrees F. This temperature and high humidity are more comfortable to the patient than the old fashioned, hot croup tent.
8. The humidity in a tent can be raised to 95 per cent when the room temperature is 70 degrees F. by the use of a mechanical humidifier.
9. The temperature and humidity of an oxygen tent have more effect on the comfort of the average patient than does the oxygen concentration.
10. Excretion of body moisture can be lessened by increasing the humidity of the room or oxygen tent if the temperature is not above 70 degrees F.
11. Tracheotomy is the operative procedure of choice.

I am deeply indebted to the staff of the Essex County Isolation Hospital for their valuable assistance in the preparation of this paper and for their cooperation in endeavoring to lower the mortality rate of this dreaded disease. For the reports of autopsies, I am indebted to Doctors Lewis W. Brown and C. L. Minier.

REFERENCES

1. Berry, Gordon: Membranous laryngitis and tracheitis with a straphylococcus aureus hemolyticus infection, Ann. Otol., Rhin. and Laryng. 37:960-962 (Sept.) 1928.
2. Baum, H. L.: Acute laryngotracheobronchitis, J. A. M. A. 91:1097-1102 (Oct. 13) 1928.
3. Brennemann, J. et al: Acute laryngotracheobronchitis, Amer. J. Dis. Children 55:667-695 (April) 1938.
4. Cassidy, W.: Acute laryngotracheobronchitis, Arch. Otolaryng. 29:857-859 (May) 1939.
5. Clerf, L. H., and Putney, F. J.: Peroral endoscopy, Arch. Otolaryng. 31:979-1005 (June) 1940.
6. Clerf, L. H.: Acute laryngotracheobronchitis, Arch. Otolaryng. 29:722-723 (April) 1939.
7. Davison, F. W.: Treatment of acute laryngotracheobronchitis, Arch. Otolaryng. 32:321-330 (Aug.) 1940.
8. Evans, M. G.: Acute laryngotracheobronchitis, Ann. Otol., Rhin. and Laryng. 48:216-226 (Mar.) 1939.
9. Felts, G. R.: Acute infective laryngotracheobronchitis, J. Oklahoma M. A. 33:9-12 (Mar.) 1940.
10. Galloway, T. C.: Postural treatment of laryngotracheobronchitis, J. A. M. A. 112:1566-1569 (April 22) 1939.
11. Gittins, T. R.: Laryngitis and tracheobronchitis; reference to nondiphtheritic infections, Ann. Otol., Rhin. and Laryng. 45:1165-1174 (Dec.) 1936.
12. Greenwood, G. J.: Acute laryngitis in infants, Ill. M. J. 75:52-57 (Jan.) 1939.
13. Hart, V. K.: Streptococcic laryngitis, Ann. Otol., Rhin. and Laryng. 36:781-785 (Sept.) 1927.
14. Johnson, Malcolm C.: Acute laryngotracheobronchitis in infants, Arch. Otolaryng. 17:230-234 (Feb.) 1933.
15. MacCready, P. B.: Acute laryngotracheobronchitis, Connecticut M. J. 4:123-126 (Mar.) 1940.
16. Negus, V. E.: An explanation of the respiratory failure sometimes occurring after a successful tracheotomy, Ann. Otol., Rhin. and Laryng. 47:608-614 (Sept.) 1938.
17. Richards, L.: Fulminating laryngotracheobronchitis, Ann. Otol., Rhin. and Laryng. 42:1014-1040 (Dec.) 1933.
18. Richards, L.: Acute laryngotracheobronchitis in children, Ann. Otol., Rhin. and Laryng. 47:326-341 (June) 1938.
19. Simpson, W. L.: Pneumothorax complicating tracheotomy in fulminating

laryngotracheobronchitis, Arch. Otolaryng. 26:411-414 (Oct.) 1937.
20. Smith, W. J.: Acute laryngotracheitis, Arch. Otolaryng. 23:420-428 (April) 1936.

DISCUSSION

LOUIS H. CLERF, M.D., Philadelphia: I am certain that all of us appreciate the seriousness of this disease and the importance of treating these patients in hospitals which have trained personnel and adequate equipment. The statistics quoted indicate that even under the most favorable conditions approximately 25 per cent of the patients die.

One of the grave handicaps lies in delayed diagnosis. Too often the family physician sees the patient late. An additional 24 hours are spent carrying out a regimen of futile treatment for croup, bronchopneumonia, or diphtheria; then the patient is rushed to the hospital.

I am heartily in accord with the plan of treatment that provides an adequate air way which must be maintained, the employment of means to cool and supersaturate the atmosphere with moisture, an adequate supply of fluids and foods, and other measures to maintain the patient's resistance at the highest level possible.

It has been my practice to employ tracheotomy promptly as soon as the indication arises; that indication is dyspnea. Too often, however, the patient is not seen until asphyxiation is imminent. Tracheotomy not only provides an air way to the trachea that is readily accessible and can be maintained, but it also makes available, means to keep open the larger bronchi.

In the earlier cases it was customary to pass a bronchoscope either perorally or through the tracheal fistula to remove crusts and secretion. Blocking of the small metal aspirating tube with tenacious crusts, which often defy removal by forceps, and the effects of trauma incident to passing the bronchoscope over inflamed musoca seem to outweigh the benefits gained. Dependence now is placed upon mechanical suction through the tracheal cannula or fistula, employing a small soft rubber tube bevelled at its end, and instilling into the trachea a quantity of sodium bicarbonate or normal salt solution without or with epinephrine hydrochloride, following which bronchoscopy is rarely necessary.

For a time, I believed that chemotherapy afforded distinct benefit. Further observations have not proven so convincing. New drugs are being discovered, and I am hopeful that something may come of these. I prefer to think of acute laryngotracheobronchitis as an acute infection of the upper part of the respiratory tract which exerts its maximum effect upon the larynx, trachea, and bronchi. If an adequate air way can be maintained, the patient probably will survive. If, however, the infection extends to the bronchioles, beyond a point where removal of obstructing crusts and secretion is possible, treatment is of no avail and death results from asphyxiation. When this condition is present, the postmortem examination usually reveals bronchopneumonic changes. From the standpoint of treatment, therefore, the most important consideration is to keep the air way open.

L. G. RICHARDS, M.D., Boston: To the best of my knowledge, this is the largest single series of cases of laryngotracheobronchitis yet presented. In view of the very obvious increase in interest in this disease which is springing up in isolated parts of the country, I think we are greatly indebted to Doctor Orton for presenting such a well rounded summary of this condition. I believe now, with improved results, we are going to run into some difficulty in establishing just what we mean by laryngotracheobronchitis, since the laryngeal inflammation tends to present a wide variety of degrees of severity, ranging from simple croup to the most severe and fulminating form of infection. The old diagnostic criteria of the necessity for tracheotomy and probability of formation of obstructive crusts which formerly constituted the diagnosis of laryngotracheobronchitis now no longer hold since some of these serious complications can often be forestalled by appropriate treatment.

I agree with Doctor Orton that intubation, except for the mildest form of infection, and particularly if it chances to be diphtheritic, is unsuitable for this condition due primarily to the risk of trauma to the larynx with subsequent stenosis. I am interested in his combination of intubation and tracheotomy carried out, as he says, to permit a certain length of time for respiratory relief before tracheotomy is performed. This argument, I believe, has some merit, although in general, all the patients upon whom I have operated have withstood tracheotomy quite satisfactorily when it has been performed with a small bronchoscope in place. It seems to me that even temporary intubation tends to be productive of subsequent trauma if the tube were left in for longer than the duration of the operation of tracheotomy. Our experience

with sulfapyridine, so far, in these patients has been apparently satisfactory. I believe that future investigation, as in the case of chemotherapy in acute mastoiditis, will center about the determination of the presence or absence in the patient's blood of immune bodies. In the latter case the value of immunotransfusion is becoming more and more apparent, and I am hopeful that in a case of laryngotracheobronchitis the same situation will hold, in which case chemotherapy will doubtless become increasingly valuable.

At the meeting in Pittsburgh of the Eastern Section of the Triological Society, mentioned by Doctor Orton, Doctor Davison and I enjoyed a friendly discussion and to some extent disagreement with regard to the use of an oxygen tent in maintaining a supersaturation of the atmosphere about the patient. My objection to the use of the tent is the confinement of the patient within a small space to which he sometimes strenuously objects, the necessity of frequent handling of the patient for purposes of suction, cleansing, feeding, and general nursing care, and the possibility of condensation within the inner surface of the tent. The objections to humidifying a small room seem to me exaggerated. The damage to surface structures in the way of paint or furniture is readily overcome by the application of aluminum paint and, so far as nursing care is concerned, it has seemed to us that it proceeds with greater facility where the patient is kept unconfined and free to play and move about in bed rather than within the narrow confines of a tent. Beyond the possible necessity for the nurses to wear rubbers in such a room, the personnel, so far as I can see, suffers no serious inconvenience. I am in full agreement with almost all of Doctor Orton's premises, his descriptions of the pathology, his interpretation of clinical symptoms, and his findings at postmortem examination. In fact, it seems as though we were both following, almost to the letter, a more or less rigid and stereotyped form of approach to the condition.

I would stress the difference in clinical appearance between a pure streptococcic laryngitis in which the epiglottis and oftentimes the arytenoids are enormously swollen, so much so as to completely hide the true cords, and the type in which subglottic obstruction is predominant and in which the supraglottic structures are little if any involved in the process. In the former instance, tracheotomy may be necessary, but it is only rarely that one sees any tendency to downward extension of the infection, and with relief of the obstruction there is usually rapid subsidence of swelling of the supraglottic structures, and immediate decannulation is possible. With subglottic obstruction, with or without accumulated crusts along the glottic walls and with little or no involvement of the supraglottic structures, one may expect a much more prolonged convalescence, possibly with inferior tracheal and bronchial inflammation and with a greater delay in the period before one can decannulate the patient.

One of the more difficult problems, particularly now that these patients are being referred to the hospital earlier by pediatricians and general physicians, is the question of the necessity of tracheotomy. Certainly in most instances a period of observation is warrantable, so long as one has at hand all the necessary means for immediate operative relief in case this becomes necessary. Under such circumstances, it is still difficult to dissuade the pediatrician from putting such patients in the old fashioned croup tent. I, myself, believe that such patients will make a far better and more rapid recovery if placed in a room with high humidity. During such a period of observation, it should in a short time become quite evident whether the respiratory infection is subsiding or not. In the latter case there is certainly no justification for delay in tracheotomizing the patient. During this period of observation, one must pay strict attention to the temperature, pulse rate, and respiratory rate, and also perhaps to a less extent to any change in the blood picture, particularly the white count. Familiar as we all are with the value of tracheotomy, there still remains an instinctive desire to avoid it and to read into the clinical picture signs of improvement at every possible opportunity. Nevertheless, once tracheotomy has been decided upon, I have yet to fail to notice a complete change in the patient's condition and the replacement of stridor, restlessness, or harsh breathing by the absolutely noiseless inspiration following relief by tracheotomy.

It is an interesting fact, which perhaps can be substantiated by those familiar with the principles of air-conditioning, that in almost every instance when the humidity of the patient's room reaches 100 per cent, the thermometer will read closely in the neighborhood of 70 degrees, regardless of the temperature of the adjoining room or outside the building.

I still cling to a type of therapy which I believe to be of great value, namely, instillation through the tracheotomy wound into the trachea of a proprietory mixture of sodium chloride, sodium carbonate, and sodium perborate as a solvent for tracheal secretions which might otherwise become inspissated and obstructive in spite of the high humidity

of the surrounding atmosphere. With such instillation it is a very simple matter for a nurse properly instructed and intelligent in this matter to insinuate a tracheal catheter practically to the bifurcation of the trachea and withdraw this solvent material with such particles of flocculent secretion with which it may be mixed. It is helpful in the introduction of this catheter to compress it in such a manner as to prevent any suction action during its passage through the upper trachea. Otherwise, it tends to adhere to the walls of the trachea, a situation which prevents its further introduction lower down where it is most needed. This may seem a simple and trivial matter, but observation of unskillful suction in this connection has convinced me that there is nevertheless a right and wrong technique for this procedure.

I must disagree somewhat with Doctor Clerf's rather pessimistic attitude toward the removal of the crusts in the trachea and lower bronchi. I believe that at times when such crusts have accumulated, mechanical removal is helpful, unless they form progressively further and further downward, or unless there has taken place an edematous thickening of the membrane, which makes their removal of no avail.

(Slide.) I should like now to show a slide illustrating our arrangement of the patient's room with the two humidifiers which we have found necessary to humidify a small room, roughly 8 by 6 feet, and preferably not more than seven or eight feet high. Incidentally, while I am not interested in their manufacture, I may say that the most satisfactory type of these humidifiers is that made by the A. C. Gilbert Company, makers of erector toys, in New Haven. The humidifier is small, efficient, and for some strange reason, decidedly inexpensive.

(Slide.) This slide indicates what one may expect within the peripheral portions of the lung in advanced cases, namely, either atelectasis with collapse of the alveolar wall or emphysema with such distention of these walls and breaking down of some of them as to suggest a flooded farmland with fragments of fencing indicating former boundaries of farms. Such is the effect of bronchial occlusion of the major air ways.

I am convinced that with earlier diagnosis, with the increasing appreciation on the part of pediatricians that these patients are suffering neither from simple spasmodic croup nor from diphtheria, with prompt reference to a hospital of a patient for whose condition immediate laryngoscopy can go far towards making a correct diagnosis, with prompt tracheotomy where indicated, with high humidification of the patient's environment, and with intelligent and skillful nursing, the former distressing mortality rate of from 30 to 50 per cent will rapidly fall, particularly if chemotherapy fulfills our hopes for it to a figure which, while perhaps not quite satisfactory, will be far more acceptable in this still serious condition than has heretofore been the case.

HORACE BELL, M.D., Belleville, New Jersey (by invitation): I cannot speak from the laryngologist's standpoint, but I can speak from the standpoint of one who has worked with Doctor Orton and other members of the hospital staff on all these cases. I certainly can verify Doctor Orton's claims regarding that which was done, and would like to add that these measures were carried out conscientiously and assiduously. He constantly has repeated to us the importance of the after-care of these patients, and he certainly taught all of us a lesson that we will not forget.

During the past year there have been more cases of laryngotracheobronchitis treated at the Essex County Isolation Hospital than, to my knowledge, have been treated in any other similar length of time in this institution. In fact, this disease has become so much more prevalent than diphtheria that we consider diphtheria out of the picture when a patient is admitted who has laryngeal obstruction, unless we do a laryngoscopy and culture diphtheria bacilli from the smears. In 1929, 1,225 patients suffering from laryngeal obstruction were referred to us in whom a diagnosis of diphtheria had been made. In 1936, there were 4 such cases. Therefore, we consider diphtheria a relatively rare disease; whereas the incidence of laryngotracheobronchitis has apparently increased markedly.

I believe that most physicians who have had experience in treating this disease advocate that the essential treatment of a patient with laryngotracheobronchitis is to relieve the mechanical obstruction to air and to administer such adequate after-treatment that the patient will continue to have an unobstructed air passage. One can readily understand from the discussions of Doctors Clerf and Richards that this subsequent unobstructed air passage cannot be maintained if a tube is kept in the larynx. By doing so, it is absolutely impossible, from the mechanical standpoint, to get the secretion up or to relieve the secretion when it plugs the bronchus.

The only reason we have used tracheal intubation is because it is a temporary expedi-

ent that will afford a little more time in which to do a tracheotomy, possibly with less discomfort. As emphasized, it gives the patient some relief from his distress and helps to overcome the so-called "respiratory shock."

Frequently, I am called to see a patient for whom something must be done immediately in the home. The patient usually is gasping for breath. Air is not entering the lungs. Not only has the patient reached the stage of cyanosis, but an ashen pallor has developed. The patient must be placed on a table and procedures taken to relieve the mechanical obstruction. Usually after a fireman has tried to resuscitate the patient, a physician is called. A tube is inserted following which immediate relief usually is obtained provided supraglottic obstruction is not present. In that case, the child does not obtain relief from the intubation, and tracheotomy must be performed. The tube is necessary until the tracheotomy can be carried out.

The mortality rate in these cases is high and will probably continue to be so, but a constant effort has been made to provide means of lowering it. That has been illustrated by Doctor Brennemann in his series of 45 cases, in which he classified the patients as having either died or been tracheotomized, or had bronchoscopic examination or intubation. He emphasizes that the aftercare of these patients is the most important factor in lowering the mortality rate. In the 9 cases in which he performed a tracheotomy, in 1938, the mortality rate was 11.1 per cent.

The treatment of laryngotracheobronchitis is a problem that concerns not only the pediatrician and the laryngologist, but the general practitioner as well. Physicians should learn to recognize this disease and its serious consequences and should refer these patients to specialists who are adequately trained and qualified to treat the condition. The patient should not be kept in the home until his condition becomes so severe that death is imminent.

Doctor Clerf condemns the use of morphine and atropine in treating patients with laryngeal obstruction. This is illustrated in the case of a ten year old boy suffering from laryngeal obstruction whom I was called to see in April. The family physician had left a supply of morphine with the parents and had advised them to administer it to the patient for the purpose of quieting him. When I arrived at 2 a.m., the child was resting, the pupils were contracted to pin-point size, and air was not entering the lungs. He had become quiet, but not because the air way passage was open. I intubated the child, and he was relieved temporarily, but he never recovered completely nor regained consciousness. At 10:40 a.m. the temperature had risen to 109, and the patient died. So, I do not believe morphine is the proper medication for patients who have any signs whatsoever of laryngeal obstruction.

I can particularly appreciate Doctor Orton's efforts and his paper, because I have seen how he works with these types of cases. I hope that this work will continue and that constant efforts will be made to decrease the mortality rate which probably can be accomplished when proper consideration is given for the after-care of the patient.

I shall not discuss the subject concerning humidifiers which Doctor Orton has mentioned. At the Essex County Isolation Hospital we instituted humidification by running hot water into the bathtub in the adjoining bathroom and obtained adequate humidity that way. This treatment is being administered now more scientifically.

THOMAS GALLOWAY, M.D., Evanston, Illinois: Doctor Orton's statistics are favorable for a large institution, and they compare favorably with any other such institution. However, where one can have such cases under direct supervision with a plan of treatment which I outlined two years ago, I think the results can be considerably improved. The last eight patients requiring tracheotomy, whom I have treated in private practice, have all recovered.

The important factor in the treatment seems to be postural irrigation and drainage. The patient's head is raised, he is turned toward the blocked side, as determined by the stethoscope, and through the tracheotomy tube 2 to 5 c.c. of a 3 per cent solution of sodium bicarbonate or normal salt solution is instilled. The patient coughs and churns this solution over the thick secretion or plugs, which are softened or loosened. The head is then lowered, and the secretion and plugs are removed by catheter suction. I seldom find it necessary to remove crusts by the bronchoscope.

It seems to me that the mechanical factors are more important in this condition than infection. Also, though what happens at the glottic level may initiate the process, what secondarily happens lower down may be more important.

In Galbreath and Steinberg's experiments, where blocking was caused by rubber plugs and primary infection was not present, a picture almost identical with acute infectious laryngotracheobronchitis was produced. Ac-

cording to Kernan and Barach, the secondary vascular effect seems the most important. With blocking of a bronchus or trachea there is a marked rise in negative intrathoracic pressure with increased blood flow to the right side of the heart and pulmonary area, but also resistance of flow toward the extra thoracic aorta. As many authors have shown, one then gets a sequence of congestion, stasis, edema, transudation, exudation, and then, by a cupping action, damage to the capillaries of the lung and even capillary hemorrhages. This provides secretions and plugs which block the lower respiratory tree and may lead to atelectasis and emphysema. By secondary infection, it may lead to pneumonitis and, if unrelieved, even to bronchiectasis and abscess of the lung.

On this conception, it is important to intervene before irreversible changes have occurred, though not before a fair trial of moist inhalations, oxygen, and rest have been given.

JOEL PRESSMAN, M.D., Los Angeles: I would like to add one or two comments to the excellent presentation of Doctor Orton, which was discussed so well, indeed, by Doctors Clerf, Richards, Galloway, and Bell.

My comment applies to tracheotomies of all sorts, but especially to tracheotomies in cases of tracheobronchitis. We must realize that when a tracheotomy tube is inserted into the trachea below the level of the larynx, the sphincter action of the larynx has been mechanically destroyed insofar as the physiology of respiration and cough are concerned. The sphincter action of the larynx is very important in the cough cycle. It momentarily closes the upper part of the respiratory tract, allowing adequate pressure to accumulate in the tracheobronchial tree. Unless this pressure does accumulate to a high degree, the cough cannot be effective in producing sputum from the lower respiratory passages. This must be realized in the postoperative care of the patient. The laryngeal sphincter cannot be replaced by adding mechanical means, but it can be strengthened by periodically administering carbon dioxide through the tracheotomy tube. When carbon dioxide is introduced, the patient develops hyperpnoea and usually a cough reaction. In some measure this helps to aerate those portions of the lungs which might otherwise become collapsed and atelectatic from retained secretions.

My second comment is stimulated by the slide showing emphysema which was demonstrated by Doctor Richards, and is best illustrated by a case report. I was called to see a child who had just such a condition of laryngeal occlusion as Doctor Richards mentioned. Pending the arrival of a surgeon to perform a tracheotomy, the family physician decided to administer artificial respiration to help the respiratory excursions. This he did, but when he vigorously pressed upon the thorax of this little child, there was no point of exit through which the air could be forced from the thoracic cavity by the manipulations of the artificial respiration, since the laryngeal outlet was closed by edema. Compression of the rib cage, therefore, increased intrathoracic pressure to the point where the emphysematous blebs, such as described by Doctor Richards, ruptured, resulting in bilateral spontaneous pneumothorax with complete collapse of both lungs, and death.

Therefore, I caution anyone who is unfamiliar with these conditions not to institute artificial respiration unless he knows there is an exit from which the air can escape other than through the wall of an emphysematous bleb and into the pleural cavity.

HENRY BOYLAN ORTON, M.D., Newark, New Jersey: I wish to thank the gentlemen for their very courteous discussions. The subject is so interesting that we could spend many hours on it.

In reply to Doctor Galloway, I did mention postural drainage.

Index photographed at the
beginning for the convenience
of the microfilm user.